

**THE BRAIN MECHANISMS  
UNDERLYING WALKING IN  
COMPLEX SITUATIONS IN HEALTHY  
OLDER ADULTS AND PERSONS  
WITH PARKINSON'S DISEASE**

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## ABSTRACT

### THE BRAIN MECHANISMS UNDERLYING WALKING IN COMPLEX SITUATIONS IN HEALTHY OLDER ADULTS AND PERSONS WITH PARKINSON'S DISEASE

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**Introduction** The ability to walk safely and independently is a fundamental component of daily living activities. Walking while dual tasking and obstacle negotiation are two tasks that have been used to investigate walking in complex situations. Deficits in cognitive domains and sensory-motor processes associated with aging and neurodegeneration impair the ability to successfully assess the environment and react to it. These changes in the ability to walk are modulated via neural circuits. However, the actual neural circuits of the brain involved in the control of locomotion in different challenging situations are still poorly understood.

**Methods** Two groups of subjects; 20 healthy older adults (mean age  $69.7 \pm 1.3$  yrs, 50% females) and 47 persons with PD (mean age  $71.7 \pm 1.1$  yrs, 32% females) were studied. The protocol included real and imagined walking while negotiating obstacles and dual tasking. Walking conditions were performed while being monitored with fNIRS and imagined walking were assessed in the MR scanner. A repeated measures design

(condition x group) was conducted with two levels; within group and between groups.

**Results** Significant differences in brain activation were observed in the fMRI and fNIRS. Between groups comparison showed that persons with PD had a significantly higher activation in frontal, parietal, occipital, and cerebellum regions during usual walking compared to healthy older adults ( $p < 0.048$ ). Comparison between the walking tasks within each group revealed (1) increased activation during walking while negotiating obstacles in both groups ( $p < 0.023$ ) and (2) increased activation during walking while dual tasking only in healthy older adults ( $p < 0.035$ ). Correlations between brain activation and performance in motor-cognitive tests were found in both groups however, healthy older adults presented inverse correlation and persons with PD positive correlation.

**Conclusions** These findings indicate that subjects with PD activate larger brain areas than healthy older adults even during usual walking. Perhaps, this increased activation is a compensatory strategy to enhance performance. The increased activation already during usual walking task may limit the ability to increase activation or recruit additional brain areas during the more complex walking tasks and may contribute to the high prevalence of falls and the dual tasking difficulty in persons with PD.

# 1 INTRODUCTION

## 1.1 Context and background

The ability to walk safely and independently is a fundamental component of daily living activities (Patla, 1998). Walking in the environment is a highly demanding task that involves the integration of sensory, motor, and cognitive processes. Sensorimotor information from visual (Donovan, Lord, McNaughton, & Weatherall, 2008; Lord, Smith, & Menant, 2010), vestibular, and proprioceptive systems along with cognitive information are continuously encoded and reassessed (Yogev et al., 2005) to select the preferable path and appropriate response. Deficits in cognitive domains and sensory-motor processes associated with aging and neurodegeneration impair the ability to successfully assess the environment and react to it. This inability to meet the demands of the environment may result in diminished independence and disability. In older adults, at least 50% of all falls are caused by trips arising from errors during obstacle negotiation (Holtzer, Stern, & Rakitin, 2004; Holtzer, Stern, & Rakitin, 2005; Marsh & Geel, 2000). Dual tasking, a necessary requirement in everyday life, involves the ability to divide attention and is mediated by executive function which are known to deteriorate with ageing and disease (Chapman & Hollands, 2007). As such, it is not surprising that older adults and persons with PD show difficulties in dual tasking and negotiating obstacles (Chen, Ashton-Miller, Alexander, & Schultz, 1994; Lowrey, Watson, & Vallis, 2007; Yogev et al., 2005).

Walking while dual tasking and obstacle negotiation are two tasks that have been used to investigate walking in complex situations (Donovan et al., 2008; Lord et al., 2010; Patla, 2001). Obstacle negotiation is a daily activity that involves the assessment of external factors as surfaces of different physical properties and obstacles that need to be avoided (Donovan et al., 2008; Lord et al., 2010; Patla, 2001; Shumway-Cook et al., 2002). Walking while dual tasking places different demands that rely on internal processes such as the ability to divide attention (Hausdorff, Schweiger, Herman, Yogev-Seligmann, & Giladi, 2008; Shumway-Cook et al., 2002; Woollacott & Shumway-Cook, 2002). Obstacle negotiation performance and walking while dual tasking are often evaluated using tempo-spatial measurements. Comparisons between obstacle negotiation performance in young and older adults revealed that older adults walk slower (Hausdorff, 2009; Maillet, Pollak, & Debu, 2012), with smaller steps (Grillner, Hellgren, Menard, Saitoh, & Wikstrom, 2005; Maillet et al., 2012), and land dangerously closer to the obstacle with their lead limb after crossing (Grillner et al., 2005; Maillet et al., 2012), increasing their risk of falls. In patients with Parkinson's disease (PD), changes in the gait pattern magnify this deterioration during obstacle crossing (Holtzer et al., 2005; Takakusaki, Tomita, & Yano, 2008). The effects of dual task on gait were found to be greater in patients than in healthy older adults (Yogev et al., 2005). While performing dual task patients demonstrate increased gait variability, reduced gait speed and lower score in the cognitive task compared to healthy older adults (Doi et al., 2013; Shumway-Cook et al.,

2002; Snijders et al., 2011; Wai et al., 2012; Wang et al., 2009; Woollacott & Shumway-Cook, 2002).

Changes in the ability to walk while negotiating obstacles or dual tasking in older adults and patients are modulated via neural circuits that include both automatic and volitional circuits (Maillet et al., 2012). A number of brain structures have been related to gait control. Supraspinal structures, such as the mesencephalic locomotor region (MLR) and the pontomedullary reticular formation, activate and regulate spinal pattern generators controlling the basic and automated step cycle (Grillner et al., 2005). At the same time higher level control centers, including the basal ganglia (BG), cerebellum, parietal and frontal cortical areas are activated to assure functional and efficient walking through the environment (Takakusaki et al., 2008). Brain imaging studies have shown multiple activation patterns during the control of gait which include the frontal cortex, supplementary motor area, lateral premotor cortex, cingulate cortex, hippocampus, parahippocampal cortex, fusiform cortex, inferior and superior parietal lobule, BG, thalamus, cerebellum, midbrain, and pons (Maillet et al., 2012). However, the actual neural circuits of the brain involved in the control of locomotion in different challenging situations are still poorly understood.

## 1.2 Problem statement

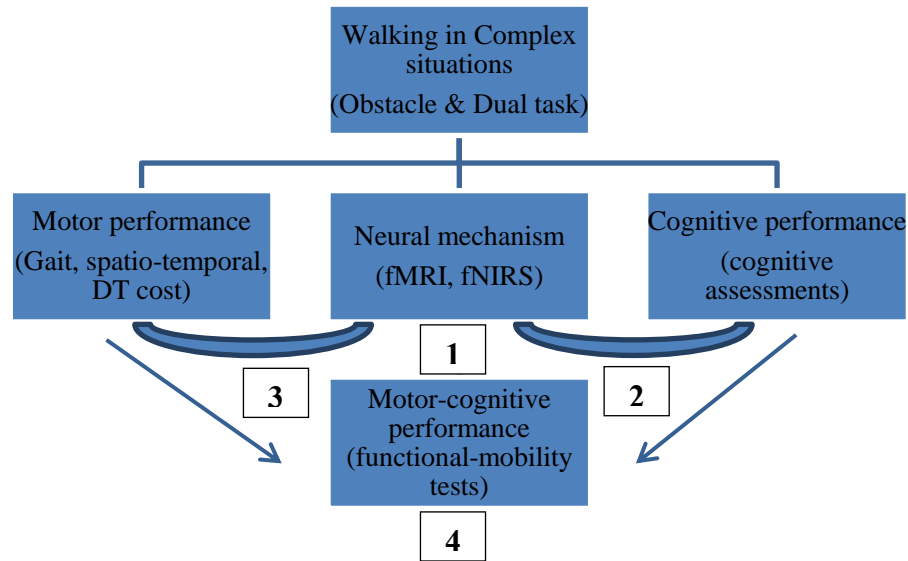
There is a growing body of research that specifically links motor and cognitive deterioration to the performance of walking in everyday life

situations. However, just a handful of studies have tried to explore the underlying neural circuits that are activated while walking in complex situations. Two studies investigated neural activation during different situations related to gait using functional Magnetic resonance Imaging (fMRI) (Peterson, Pickett, Duncan, Perlmutter, & Earhart, 2013; Wai et al., 2012) and two studies investigated frontal activation during walking while dual tasking using functional Near-Infrared Spectroscopy (fNIRS) (Doi et al., 2013; Holtzer et al., 2011). The studies have presented information regarding the brain areas activated during complex motor tasks as stepping over obstacle, turning and dual tasking however several questions remain that form the basis for this proposal. The protocols used included only one complex condition, either an obstacle course that involves assessment of external factor or a dual task paradigm that rely on internal processes, and did not assess the complexity of the tasks and their different influence on brain activation. In addition, none used both fMRI and fNIRS as complimentary methods to assess real and imagine walking in complex situations. As such, additional studies are needed to evaluate the neural mechanisms underlying walking in complex situations and more specifically examine the alterations in neural circuits possess by different situations. We believe that a better understanding of these neural mechanisms will potentially impact clinical care. It will allow the development of explicit interventions that address specific deficits while increasing independence in everyday life. Therefore, the present study will address the following four goals.



### 1.3 Goals of study

1. To investigate the neural mechanisms underlying walking in different complex situations as obstacle negotiation and dual task in (1) healthy older adults and (2) persons with PD using imaging techniques (fMRI and fNIRS), and to evaluate the differences between these two cohorts (Figure 1).
2. To examine the association between cognitive performance (as examined by computerized and neuropsychological tests) and neural mechanisms underlying walking in complex situations in (1) healthy older adults and (2) persons with PD, and to evaluate the differences between these two cohorts (Figure 1).
3. To evaluate the relationship between motor performance of walking in complex situations (as examined by the distance of the trial and leading legs from the obstacles and dual task cost) and neural mechanisms in (1) healthy older adults and (2) persons with PD, and to examine the differences between them (Figure 1).
4. To test if motor-cognitive assessments (as examined by functional-mobility tests) can predict performance of walking in complex situations in (1) healthy older adults and (2) persons with PD, and to evaluate the differences between them (Figure 1).



**Figure 1:** Goals of the study

1) Refers to the first goal of the study in which the underlying neural mechanisms will be assessed. 2) refers to the second goal in which the association between cognitive performance and neural activation will be evaluated, 3) refers to the third goal in which correlation between tasks performance and neural activation will be assessed, and 4) refers to the ability of motor-cognitive functional mobility tests to predict the performance of complex task.

#### 1.4 Operational definitions

In order to better develop the hypotheses, the operational definitions are presented for each goal separately. The following relate to

##### **goal 1:**

1. Complex situations: Eight dimensions will be included to increase complexity: 1) distance, 2) temporal characteristics, 3) ambient conditions (light and weather conditions), 4) terrain characteristics, 5) physical load, 6) attentional demands, 7) postural transitions, and 8) density (number of people and objects in the immediate environment). The complexity of the walking situations will include

internal processes reflected by dual task and external factors reflected by different obstacle dimensions. Performance of walking in a complex situation will be compared to walking in a straight, uncluttered path reflecting walking in a simple situation (Donovan et al., 2008; Shumway-Cook et al., 2003; Tan, Danoudis, McGinley, & Morris, 2012).

2. Neural mechanisms: Refer to structures such as neurons, neural circuits and regions of the brain that regulate behavior, voluntary and involuntary systems. Neural mechanisms will be investigated by measuring neural activation using fMRI and frontal lobe activation using fNIRS. Description of these tools is provided in chapter 3.

The following relate to **goal 2**:

1. The cognitive assessments involve a variety of cognitive measures that play an important role in gait. Cognition is defined as a group of mental processes in several domains including attention, memory, producing and understanding language, learning, reasoning, problem solving, and decision making. Cognition will be assessed using: (1) Trail making test a&b (TMTa, TMTb), and (2) a computerized cognitive battery (Mindstreams; NeuroTrax NeuroTrax Corp, Newark, NJ) that generates composite indices of six cognitive domains: (1) cognitive global score (CGS), (2) memory, (3) executive function (EF), (4) visual spatial (VS), (5) attention, and (6) information processing (IP). Scores are

represented similarly to an IQ-like scale, with 100 representing the estimated population mean normalized for age and education.

The following relate to **goal 3**:

1. Spatio-temporal measurements describe motion in terms of position and time. In this study spatial-temporal parameters that will be analyzed include step length, step and stride time, stance and swing durations and related variability (Hausdorff, 2009).
2. Obstacle negotiation task will include negotiating physical obstacles placed on the ground while making the necessary gait adjustments to safely clear the obstacles. Obstacle negotiation performance will be measured using three dependent variables: (1) trail leg distance from obstacle, (2) leading leg distance from obstacle (landing), and (3) duration of standing on one leg while stepping over an obstacle.
3. Dual task (DT) will include the performance of two tasks simultaneously namely motor and cognitive. The cognitive task chosen will be serial subtraction. During this task subjects will be asked to serially subtract 3's from a predefined 3 digit number. The task will be performed as a single-task (ST) (while standing) and as a DT while walking. When performance on either the cognitive and/or motor tasks are worse when conducted simultaneously as compared to separately, these two tasks interfere with each other, and are assumed to compete for the same class of information processing resources in the brain (Wickens, 1991). Interference is often assessed as the cost of the cognitive task on specific gait

measures such as gait speed, stride length and gait variability. In this study, dual task cost will be calculated as a percent according to the equation:  $((ST-DT)/ST) \times 100$ .

The following relate to **goal 4**:

Functional and mobility measurements include two tests that evaluate different aspects of balance, mobility and function related to motor-cognitive aspect. These performance-based measures include: (1) Four step square test (FSST) and (2) MiniBEST (Mini Balance Evaluation Systems Test).

## 1.5 Hypothesis

The following four hypotheses correspond to the four goals of the study. Each hypothesis will address two levels of analysis: (A) condition effects (within group) and (B) between groups differences.

1. (A) Increased activation will be observed in both complex walks in prefrontal areas including the SMA and the superior and middle frontal gyrus, and parietal areas including the precuneus and inferior parietal lobe (IPL). These brain areas are referred to as the “fronto-parital network”. Comparison between conditions will demonstrate different activation intensities and locations. During the DT walk, prefrontal areas will be more activated while during the obstacle walk, activation will be intensified in the parietal areas. In addition, walking with obstacles will also activate the “visual-motor” network that

encompasses occipital areas such as the inferior and middle occipital gyrus.

(B) Higher neural activity will be observed in the above networks in persons with PD as compared to healthy older adults. In addition, patients will demonstrate more activation in the visual-motor network representing compensatory mechanisms, than healthy older adults.

2. (A) I hypothesize that an inverse correlation will be observed between performance in cognitive tests and neural activation of the prefrontal cortex. For example, subjects that will score higher (i.e., better) in the cognitive tests will show lower neural activity in prefrontal areas during DT walk. Similarly, subjects that will score lower in the cognitive tests will show higher neural activity in prefrontal areas during performance in both obstacle and DT walk.

(B) Persons with PD will score lower than healthy older adults on the cognitive tests and therefore will present higher neural activation in prefrontal areas representing an increase effort.

3. (A) Better motor performance in complex situations will be inversely correlated to neural activation. Better obstacle crossing measured by the distance of the trial and leading legs from the obstacles and the duration of single limb stance during obstacle crossing will be inversely correlated to neural activation in prefrontal, parietal, and occipital areas; referred as the “parieto-frontal” and “visual-motor” networks. Increased DT cost in gait speed will be correlated with lower neural activation in prefrontal areas associated with the “attentional network”.

(B) The distance of the trial and leading legs from the obstacles will be shorter in persons with PD than in healthy older adults reflecting impaired performance during the obstacle course. Persons with PD will also have higher DT cost. These differences will result in increased neural activation in prefrontal, parietal, and occipital areas reflecting amplified recruitment of neural areas during both complex situations.

4. (A) Lower performance on motor-cognitive functional mobility tests will predict the performance in both obstacle and DT walks.

(B) Persons with PD will display lower performance on motor-cognitive functional mobility tests than healthy older adults.

## 1.6 Significance and need for the study

Investigating gait in a sterile, simple environment lacks the complexity required for negotiating everyday life conditions and therefore provides limited information regarding walking ability. Two lines of research have been used in the literature to investigate walking in complex situations; one evaluates task performance and the second assesses the motor-cognitive status as it may reflect on performance. However, few attempts have been made to gain insight into the underlying neural mechanisms that act as mediators between motor-cognitive status and performance of a task. A novel aspect of this study involves the assessment of neural activation while performing two different complex activities; one involves assessment of external factors and one rely on internal processes.

Investigating neural mechanisms of gait is challenging as the methods often used to examine brain activation do not involve assessment during actual walking. Therefore, additional novel aspect of this study is the use of two complementary methods, functional magnetic resonance imaging (fMRI) and functional Near Infra-red Spectroscopy (fNIRS) to examine neural activation during walking in complex situations. The use of fMRI to better understand cortical control of gait increased tremendously in the recent years with the introduction of imagined locomotion as a novel paradigm to study brain activation during motor tasks<sup>40</sup>. The use of fNIRS as a complementary neuroimaging method allows the measurement of frontal lobe activation while performing actual walking.

The potential of this study is huge as the understanding the neural mechanisms underlying walking in complex situations may shed light on possible interventions that will increase function, independence and reduce disability.



## 2 LITERATURE REVIEW

### 2.1 Introduction

The purpose of this literature review is to provide the background knowledge to serve as the basis for the proposed research and to identify gaps in the literature that will be filled by the proposed research. Specifically, the literature was reviewed to reflect three relevant areas addressing the goals of the study: 1) walking in complex situations, 2) gait and cognitive deficits in healthy elderly and persons with PD; and 3) Neuroimaging of walking using fMRI and fNIRS.

Mobility has been defined as the ability to move independently from one location to another and is an essential component of most activities of daily living (Shumway-Cook et al., 2003). Successful mobility depends on the task complexity (Donovan et al., 2008; Patla, 1998; Shumway-Cook et al., 2002) and the subject's skills and abilities. The interactions between these factors determine a threshold; once exceeded, mobility is interrupted and the target goal will not be reached. In the context of this work, complexity will be assessed using two highly demanding tasks; walking through an obstacle course and walking while dual tasking. Obstacle negotiation represents a complex task, which requires the assessment of external factors necessitating the integration of multiple systems such cognitive, visual, perceptual and motor. Dual task performance represents an attention-demanding task that involves internal processes (Chapman & Hollands, 2007; Chen et al., 1996; Hausdorff et al., 2008; Holtzer, Wang, &

Verghese, 2013; Lowrey et al., 2007). Although walking has long been considered a primarily automatic motor task, emerging evidence suggests that this view is overly simplistic. Walking in the real world requires paying attention to various environmental features and recovering from postural perturbations to avoid stumbles or falls.

With aging and neurodegeneration, sensory integration deteriorates increasing the incidence of failure in mobility often resulting in a high risk of falls. Approximately 30% of people over age 65 fall each year (Campbell et al., 1990; Hausdorff, Rios, & Edelberg, 2001). The incidence of falls further increases with approximately 40% of those over age 80 experiencing one or more falls each year (Campbell et al., 1990; Deandrea et al., 2010). In persons with PD, the incidence of falls is even higher ranging from 37-68% (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001; Koller, Glatt, Vetere-Overfield, & Hassanein, 1989; Buccello-Stout et al., 2008; Davidsdottir, Wagenaar, Young, & Cronin-Golomb, 2008; Galna et al., 2012; Hausdorff et al., 2008; Koller et al., 1989; Rogers, 2006; Yogev et al., 2005). Therefore, this cohort selected as they represent a population that suffers from motor and cognitive deficits.

The inter-relationship between cognitive deficits and gait disturbances has been attributed to specific brain networks such as the prefrontal-parietal and cingulate areas that are selectively affected by disease that accompany but are not necessarily caused by aging per se. However, just handful of studies examined the underlying neural

mechanisms related to walking in complex situations and none assessed the differences in neural activation associated with task complexity. fMRI is considered the gold standard to evaluate neuronal activity during task performance. To assess complex situation in an fMRI paradigm, motor imagery tasks of walking and virtual reality scenarios will be examined as tools to assess neural activation. However, these tasks although similar do not accurately reflect the task of walking. In the recent years a number of studies used functional Near Infra-red Spectroscopy (fNIRS) to measure neural activation while performing actual walking (Doi et al., 2013; Holtzer et al., 2011). As such, fNIRS can be used as a supplementary neuroimaging assessment to fMRI in order to obtain direct evidence on frontal activation during actual walking in complex situations.

The chapter will cover the above topics to form the basis for the design of this study.

## 2.2 Methods

An electronic search was conducted using Medline and CINAHL databases. The search was restricted to manuscripts written in English. There was no limitation of publication date or restriction by study design. The terms that were mapped and combined included: gait, ambulation, complex environment, everyday life environment, navigation, sensory-motor system, visual system, visual-spatial, cognitive system, healthy elderly, normal aging, gait deficits, gait impairment, cognitive deficits, cognitive impairment, Parkinson's Disease (PD), obstacle course,

obstacle negotiation, tempo-spatial measurements, dual task, navigation, neural mechanism, neural substrate, MRI, fMRI, motor imagery, mental practice, virtual reality, virtual environment, functional Near Infra-red Spectroscopy (fNIRS). A study was eligible for inclusion in the review if it met the criteria of studying gait in healthy elderly and persons with PD populations. Studies were excluded if they were not directly related to gait or posture.

The initial results were supplemented by grey searching articles in the reference lists. Articles that appeared to meet the criteria for inclusion were obtained and reviewed. 175 articles were chosen to be included in this review. Articles selected for this review focused on three main areas in line with the goals and hypothesis formulated in this proposal (Figure 1): (1) walking in complex situations such as obstacle course and dual tasking, (2) Gait and cognitive deficits in healthy older adults and persons with PD, (4) Neuroimaging of walking using MRI and fMRI.

## 2.3 Complex walking situations

The environments that we routinely encounter at home and within our community are complex. These environments continuously challenge us to adapt our balance control and walking patterns to surfaces of different geometrical and physical properties as well avoid moving and static obstacles. In addition, overall planning of path selection based on prior cognitive maps, navigation, divided attention and visual scanning are required for successful mobility in these environments (Donovan et al.,

2008; Patla, 1998; Shumway-Cook et al., 2002; Shumway-Cook et al., 2003).

Two paradigms that were vastly investigated in the literature to illustrate walking in complex situations are obstacle negotiation and dual task walking. Obstacle crossing is a daily activity that involves tasks such as going up a curb or stepping over a crack in the ground or a branch. Studies have shown that in older adults at least 50% of all falls are caused by trips arising from errors during obstacle negotiation (Donelan & Pearson, 2004; Galna et al., 2012; Lord, Rochester, Hetherington, Allcock, & Burn, 2010). Obstacle crossing has 3 phases: (1) pre-crossing, (2) crossing, and (3) landing after crossing/recovery (Chen, Ashton-Miller, Alexander, & Schultz, 1991). Each phase has been assessed according to sensorimotor and cognitive demands whereas the pre crossing phase is considered more attentionally demanding (Chen et al., 1991; Galna, Peters, Murphy, & Morris, 2009) and crossing and recovery phases are considered more sensorimotor demanding (Said et al., 2005). Difficulty in one of these phases may lead to a trip and subsequent fall (Chen et al., 1991; Said et al., 2005).

During each of these phases the leading and trailing limb trajectories have been measured using spatial and temporal variables. Spatial measures include the distance from limb placement to obstacle for pre crossing phase, the height of limb from obstacle for crossing phase, and the distance from obstacle to limb placement for recovery phase.

Temporal variables provide information about the time required to modify limb trajectories. Pre-obstacle swing time, from toe-off to obstacle clearance, provides information about the time required to prepare the limb for clearance. Post-obstacle swing time, from obstacle clearance to foot contact, provides information about the time required to prepare the limb for landing (Chen et al., 1991; Said et al., 2005).

Cognitive aspects of obstacle negotiation that were mainly discussed in the literature are attention and visual-spatial ability. That is probably because avoiding obstacles in a dynamic environment requires (1) selective attention to relevant stimuli, (2) maintain high levels of attention for long periods of time, and (3) correct perception of obstacles dimensions (Jaap, 2005; Kovacs, 2005). Numerous studies demonstrate that successful obstacle crossing is compromised when participants are required to perform simultaneously an additional cognitively demanding task (Brown, McKenzie, & Doan, 2005; Chen et al., 1991; Weerdesteyn, Schillings, van Galen, & Duysens, 2003). These compromised motor performance shows that obstacle negotiation stresses the availability of cognitive resources. In addition, it was shown that visual information as obstacle size, obtained several steps before the obstacle, is used for feed-forward planning of the negotiation of the obstacle (Patla & Goodale, 1996; Patla & Vickers, 1997). This suggests that visual acuity at a distance of several meters may be crucial for successful performance.

Many studies have investigated whether gait in complex situations requires attention by using different dual tasking paradigms (Hausdorff et

al., 2008; O'Shea, Morris, & Iansek, 2002; Springer et al., 2006; Yogev-Seligmann, Hausdorff, & Giladi, 2008; Yogev et al., 2005). Dual tasking costs or difficulties in the simultaneous performance of two or more tasks have been explained by three possible neuropsychology theories; the capacity-sharing theory, the bottleneck theory and the multiple resource models theory (Pashler, 1994; Wu & Hallett, 2008). The capacity-sharing theory suggests that attentional resources are limited in capacity, and therefore the performance of two attention-demanding tasks will cause deterioration of at least one of the tasks. Thus, the performance of an additional task during walking alters gait parameters or execution of the second task or both. The bottleneck theory proposes that a bottleneck occurs when two tasks are concurrently processed by the same neural network. As such, the processing of the second task will be delayed until the network is free from processing the first task. According to this theory, performance of another task during walking might result in a slower gait or delayed performance of the second cognitive task, but only if the neural networks involved in the two processes overlap (Pashler, 1994; Wu & Hallett, 2008). The multiple resource models suggest that processing may need a number of resources. For example, one of the models claims that if two tasks don't share common resources dual task cost won't be observed, while other model, the cross talk model, argues that if both tasks are from a similar domain dual task cost won't be observed (Pashler, 1994; Wu & Hallett, 2008). Nevertheless, neuroimaging studies have been

interpreted to support all three models and at present, there is no consensus on the theory that best explains dual tasking costs.

In this study two different paradigms of dual tasking will be included to better fit the two imaging methods constraints. In the MRI scanner the dual task paradigm will include imagined walking while navigating to specific target as any other cognitive task will not allow motor imagery of walking. Navigation is considered a highly cognitive demanding task that requires attention, planning, memory, and decision-making, all considered different domains of executive function (Jordan, Schadow, Wuestenberg, Heinze, & Jancke, 2004; Zhang, Copara, & Ekstrom, 2012). On the other hand, the fNIRS walking assessment will be performed in a corridor of 20 meters which will not allow navigation. Therefore, the fNIRS assessment will include dual task paradigm of walking while serially subtracting 3s (Hausdorff et al., 2008; O'Shea et al., 2002; Springer et al., 2006; Yogev-Seligmann et al., 2008; Yogev et al., 2005).

Numerous of studies have established that walking in complex situations can be compromised in older adults limiting their mobility and independency in the community (Deandrea et al., 2010; Menant, St George, Fitzpatrick, & Lord, 2010; Rochester et al., 2004). Kovacs and Van Dieen et al found that age related deficits in vision, proprioception, visual-spatial ability, and attention may have negative impact on walking in complex situations (Jaap, 2005; Kovacs, 2005). These deficits and their impact increase exponentially with neurodegenerative disease as Parkinson disease (PD).



## 2.4 Motor-cognitive deficits in older adults & persons with PD

### 2.4.1 Healthy older adults

Normal aging is associated with declines in several physiological systems including musculoskeletal, visual, vestibular, proprioception, coordination, postural responses and cognitive function. All of these play an important role during walking in everyday life and therefore responsible for the changes observed during walking in complex situations.

Number of changes in tempo-spatial measurements has been demonstrated during obstacle crossing in healthy older adults compared to healthy young. A slower crossing speed over an obstacle has been observed, representing an attempt to minimize the speed of the lower extremities and momentum produced during the movement. An increase in momentum may make it more difficult to control the lower extremities and increase the chances of a loss of control during the step. Shorter step lengths was also observed suggesting that healthy elderly attempt to minimize the time spent in single support, as single support represents the most unstable period of time during gait and stepping. As a result a shorter obstacle-heel strike distance was observed demonstrating the reduced balance abilities (Kovacs, 2005; McFadyen & Prince, 2002; Medell & Alexander, 2000). An additional tempo-spatial measurement observed in healthy older adults was the reduced gait velocity when approaching an obstacle. It was suggested that by decreasing their gait velocity they will control the momentum created by the movement of the body as they

approach the object (Kovacs, 2005). Although many differences in tempo-spatial measurements have been shown between healthy young and healthy older adults, the literature does not convincingly show that these changes are the major factors responsible for tripping in the elderly.

Another cognitive component shown to be important when stepping over an obstacle is the visual-spatial domain. It was shown that the acquisition and storage of visuo-spatial information regarding the surrounding environment is critical for generating corrective stepping in response to predicted and unpredicted obstacles appear in the way (Lord et al., 2010). However, healthy elderly tend to generate eye movement toward, and then spend greater time looking at, a target location when compared with healthy young (Lord et al., 2010). It is probably used as a strategy to maximize the amount of time they spend in acquiring and storing visuo-spatial information about the environment to plan subsequent stepping movements (Lord et al., 2010).

Aging is also associated with decline in executive function including attention, problem solving, information processing, and awareness of self and surrounding environment, components that apparently have important impact on walking and navigating in complex situations (Alexander & Hausdorff, 2008; Ambrose, Paul, & Hausdorff, 2013). As such, it is not surprising that healthy elderly may show difficulties in dual tasking, in general, and when walking while performing another task, in particular (Holtzer et al., 2004; Holtzer et al., 2005). Numerous of studies investigate the effects of dual tasking on gait in healthy elderly. Their findings

demonstrate that similar to healthy young the performance of cognitive task while walking reduces gait speed and increases the reaction times of the cognitive tasks. Although there may be some deterioration in the performance of the cognitive task that tends to increase with aging, no other changes in gait patterns were observed. This demonstrates that gait stability is generally not affected by dual tasking in healthy older adults (Sparrow, Bradshaw, Lamoureux, & Tirosh, 2002; Springer et al., 2006; Yogev-Seligmann et al., 2008).

#### 2.4.2 Persons with PD

Neurodegenerative diseases as Parkinson disease, which are associated with limited cognitive or/and motor resources will demonstrate increased difficulty to walk in complex situations (Hausdorff et al., 2003; Yogev et al., 2005). Parkinsonian gait is described as slow gait with decreased or absent of arm swing, longer double limb support, shortened stride length and impaired postural control (Blin, Ferrandez, & Serratrice, 1990; Yogev et al., 2005). These changes in gait pattern have a direct impact on the ability of persons with PD negotiate obstacle (Hausdorff, 2009; Lord, Ward, Williams, & Anstey, 1993).

Recent research has shown that persons with PD approach and step over obstacles slower, with smaller and widener steps than healthy elderly, while also spending more time in double limb support (Galna, Murphy, & Morris, 2010; Vitorio, Pieruccini-Faria, Stella, Gobbi, & Gobbi, 2010). However, clearance of the leading and trailing foot wasn't shown to

be different between persons with PD and healthy elderly probably because persons with PD use the obstacle as an extrinsic cue to regulate their foot clearance (Galna et al., 2010). The fact that persons with PD take more time to step over the obstacle and spend more time in double limb support than healthy elderly reflect their difficulty to move feet faster due to hypokinesia. In addition, it was suggested that persons with PD widened their step when crossing the obstacle to compensate for postural instability in the frontal plane (Galna et al., 2010; Stegemoller et al., 2012).

During the pre-crossing phase persons with PD demonstrate poor planning of the trail foot placement in front of the obstacle. They are more likely to place their trail foot too far from the front of the obstacle given their short step length, causing them to land either on or close to the obstacle with their lead heel. In addition it was shown that patients with more severe PD symptoms are more likely to step on obstacle, walk slower, and land closer to the edge of the obstacle after crossing compared to mildly affected patients (Galna et al., 2010; Stegemoller et al., 2012). These changes in spatio-temporal measurements during obstacle crossing in persons with PD reveal that they adapt a more conservative strategy when negotiating obstacles.

In addition, visuo-spatial deficits are common in PD and manifest as an inability to perceive obstacles and negotiate varying terrain. Recent models suggest that visuo-spatial deficits in persons with PD may be related to the crucial role of the caudate nucleus in route learning and the hippocampus in allocentric navigation (Galna et al., 2012). These findings

suggest that less frequent visual sampling while walking in complex environments contribute to the visuo-spatial deficits seen during walking in persons with PD.

Cognitive impairments have been strongly linked with PD. It is estimated that 19–30% of people with early, newly-diagnosed PD present with cognitive impairments (Kelly, Eusterbrock, & Shumway-Cook, 2012; Muslimovic, Post, Speelman, & Schmand, 2005) which worsen with disease progression (Muslimovic et al., 2005). Numerous studies have documented deficits in complex attention and frontal executive functions in persons with PD (Bohnen et al., 2006; Muslimovic, Post, Speelman, & Schmand, 2007; Tamura, Kikuchi, Otsuki, Kitagawa, & Tashiro, 2003). Persons with PD perform more poorly on measures of divided attention, planning, response inhibition, working memory, mental flexibility, and abstract reasoning (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009; Bohnen et al., 2006; Watson & Leverenz, 2010). This deterioration in executive function was found to be associated with deficits in walking in complex situations (Lord et al., 2010; Plotnik, Dagan, Gurevich, Giladi, & Hausdorff, 2011). For example, poor performance in the Trail Making Test (TMT) which measure the ability to alternate between two tasks quickly and accurately was associated with low physical performance in dual task TUG, stair climbing and obstacle negotiation gait (Hirota et al., 2010). In addition, it was demonstrated that gait impairments in persons with PD are exacerbated under cognitive load as dual-task conditions.

Persons with PD have increased demands placed on central processing resources because of the need to cognitively attend to the ongoing execution of movement such as walking, which was previously controlled by more automatic motor control mechanisms (Vandenbossche et al., 2012). This increased need to think about walking requires attention, which is a limited cognitive resource especially in persons with PD that demonstrate deficits in EF and attention. Increased difficulties with dual-task performance because of the need to concentrate on two tasks simultaneously can place further pressure on those limited attentional resources in persons with PD. In addition, the loss of walking automaticity is accompanied with motor and cognitive impairments which further stress this limited attentional capacity.

In contrast to healthy elderly, when persons with PD perform cognitive task while walking, changes in gait patterns are observed. These gait alterations include slower gait speed, shorter strides, increased double support time, and increased stride-to-stride variability (Hausdorff, 2009). Furthermore the severity of dual-task interference during gait may be related to the degree of difficulty of the secondary task (O'Shea et al., 2002). Situations in which the secondary task is complex occur in everyday activities and therefore pose considerable problems with functional activities that involve walking in everyday life environments (Rochester et al., 2004).

In summary, obstacle course and dual task will be the two paradigms used in this study to illustrate situations of walking in complex

situations. As widely described in this review, these tasks require high motor and cognitive demands which were mainly quantified by measuring spatio-temporal measurements and/or evaluating the association between performance in cognitive tests and motor functional tests. However, these measurements provide limited knowledge regarding the neural mechanisms associated with walking in complex situations. Exploring these neuronal mechanisms will improve our ability to provide adequate intervention that will increase function, independence and reduce disability.

## 2.5 Neuroimaging of walking using MRI and fMRI

The neural mechanisms of walking have been assessed using different neuroimaging techniques. Magnetic resonance imaging (MRI) has been vastly used in many disciplines to explore different neural mechanisms associated with motor, cognitive, and affective behaviors. However, using this technique to explore motor behavior as gait is limited because of the restricted movement allowed in the MRI scanner. During the MRI scan the subject lies on his/her back with the head placed in the head coil, ensuring that minimum movement of the head is possible. As such, examination of motor behavior related to gait is possible in the form of motor imagery (MI) in which the subject is asked to imagine he is walking or by imitating patterns of gait that include alternate movements of feet. Although both methods involve activation of neural circuits related to gait there are still many components of gait that are compromised. Therefore,

additional neuroimaging methods such as functional Near-Infrared Spectroscopy (fNIRS), have been suggested.

### 2.5.1 MRI and fMRI

Magnetic Resonance Imaging (MRI) is a non-invasive imaging method. It enables one to see the anatomy of the human brain without surgical intervention. The MRI scanner uses a high magnetic field (usually 1.5 or 3 Tesla) in order to perform the scan. The scanner detects the hydrogen nuclei of water molecules (which are in fact single protons) in our body. During a scan, radio waves are transmitted to the subject synchronizing the phases of all protons' spins. After a short time ( $< 1$  s) most protons release that energy back in the form of radio waves which are picked up by detectors within the scanner. The time it takes the protons to release that energy is different depending on the tissue (white or grey matter, ventricles etc.) and this forms the basis for the MRI signal.

Alterations in neuronal activity are accompanied by physiological changes in cerebral blood flow (CBF) (Fox et al., 1986), blood volume (CBV) (Belliveau et al., 1991; Fox & Raichle, 1986), blood oxygenation (Fox & Raichle, 1986; Fox, Raichle, Mintun, & Dence, 1988), and metabolism (Phelps, Kuhl, & Mazziota, 1981; Prichard et al., 1991). A new technique was then developed called functional magnetic resonance imaging (fMRI) which besides providing anatomical structure maps, has the ability to observe which brain structures modify their activity as subjects receive sensory stimulations or carry out given tasks, such as



moving a finger or viewing pictures (Belliveau et al., 1990; Belliveau et al., 1991; Ogawa, Lee, Kay, & Tank, 1990; Ogawa et al., 1992; Ogawa et al., 1993).

The fMRI technique measures signal changes due to inhomogeneities of the magnetic field, resulting from changes in blood oxygen levels. The basic principle of this technique lies in the fact that oxyhemoglobin (the oxidized form of a molecule found in red blood cells) is a diamagnetic molecule, but when it gives up its oxygen it becomes deoxyhemoglobin, which is a paramagnetic molecule. The presence of such paramagnetic molecules in the blood causes a change in blood vessel magnetic susceptibility, creating a difference between the vessel before and after it disposed of the oxygen and thus distinguishes it from the surrounding tissue (Belliveau et al., 1991; Ogawa et al., 1990; Ogawa et al., 1992; Tank, Ogawa, & Ugurbil, 1992). This effect produces inhomogeneity in the magnetic field, which results in a decrease of the blood oxygen level dependent (BOLD) fMRI signal (Heeger & Ress, 2002).

Neuronal activity increases blood flow in the vessels of active regions. Although the exact mechanism that causes this increase remains elusive (Attwell et al., 2010; Heeger & Ress, 2002; Iadecola, 2004; Iadecola & Nedergaard, 2007; Takano et al., 2006), the result is a large decrease in the local level of deoxyhemoglobin, as oxygen extraction remains stable at that time (Fox & Raichle, 1985). What makes fMRI so attractive is that it is a high spatial resolution non-invasive technique. Its spatial resolution is usually in the order of 1.53 mm. However, the main

disadvantage of this technique is its poor time resolution (2-4 s), due to the fact that the BOLD signal response is inherently significantly slower than the underlying neuronal activity (Horwitz, Friston, & Taylor, 2000).

In a typical fMRI experiment each measure, called volume, contains a number of 3D slices, about 3-4 millimeters thick. Each slice consists of a number of voxels (a pixel with a volume) that represents the intensity of the BOLD signal. The change in BOLD signal over a series of 3D images creates a time course for each voxel. When a neuronal action occurs, the BOLD signal time course is referred as the Hemodynamic Response Function (HRF) which has a known shape. The HRF comprises three steps (Heeger & Ress, 2002); The fMRI signal initially decreases, as active neurons use oxygen, thereby increasing the relative level of deoxyhaemoglobin in the blood. This decrease, however, is very small and is not always found (Ugurbil, Toth, & Kim, 2003). The next step is a large signal enhancement attaining its maximum after approximately 6 sec. This increase is due to a massive oversupply of oxygen-rich blood. The final step is a slow return to normal deoxyhaemoglobin levels. The signal decays after an initial undershoot and, after approximately 24 sec, it reaches its original baseline level (Heeger & Ress, 2002).

The fMRI method can be used to explore neural mechanisms related to walking in complex situations by providing information regarding brain activity. As mentioned before the MRI environment doesn't allow direct assessment of gait movement, therefore MI has been suggested.

### 2.5.2 Motor Imagery

Motor imagery (MI) refers to the mental performance of an action without an overt movement (Beauchamp, Petit, Ellmore, Ingeholm, & Haxby, 2001; Holmes & Calmels, 2008). Imagery like all other cognitive functions is not a single, undifferentiated ability. Rather, it arises from the joint action of numerous systems which may vary depending on the precise type of task being performed (Zacks, 2008). MI is a highly complex mental process that involves variety of cognitive components including retrieval of information from long term memory to working memory, visual-spatial working memory, arousal, attention and concentration. It is considered as a neural network generation involving primarily top-down sensorial, perceptual and affective brain areas (Holmes & Calmels, 2008; Zacks, 2008). MI shares a number of mental operations and relies on common neural structures (Grezes & Decety, 2001). These structures are analogous to some of those that are active during the preparation, anticipation, and, in some cases, actual production of actions (Holmes & Calmels, 2008).

Cerebral regions involved in the processing of mental images include two main regions; the parietal and the frontal regions in which form the parieto-frontal network (Hetu et al., 2013). MI includes three aspects: (1) spatial aspect, which relates to the environment in which the task take place, (2) movement aspect which relates to the task itself, and (3) affective aspect which relates to the emotions being raised.

Spatial aspects are controlled and tested using different environment images that are presented in the scanner (Gabbard, Cacola, & Cordova, 2011; Saimpont, Mourey, Manckoundia, Pfitzenmeyer, & Pozzo, 2010; Saimpont, Malouin, Tousignant, & Jackson, 2013; Snijders et al., 2011). For example, Snijders et al presented several photographs of walking trajectories each of different width to examine spatial aspects of gait during MI (Snijders et al., 2011). Spatial representation yielded activation in three components of the parieto-frontal network; the first component includes the intraparietal sulcus, the second involved the depth of the superior frontal sulcus, and the third corresponds to the pre-Supplementary Motor Area (SMA). The parahippocampal gyrus cortex has been shown to be specifically involved in the perception and mental imagery of spatial scenes and places (Epstein, Harris, Stanley, & Kanwisher, 1999; Janzen & van, 2004). In this proposed study we suggest to use virtual environment (VR) to create the scene in which subjects imagined themselves walking.

Specific aspects of movement were tested by emphasizing different components of gait. For example, imagine walking while navigating to a specific target and imagine stepping over an obstacle. These different tasks demonstrated increased activation in the SMA and premotor cortex (PMC) (Guillot & Collet, 2005; Holmes & Calmels, 2008). In contrast, activation of primary motor cortex (M1) during MI was not always demonstrated. It seems that a variety of components, such as instructions for MI, imagery ability, and motor expertise can influence the activation of

M1. However, even though M1 may be involved in MI its activation will be less than during real motor execution(Holmes & Calmels, 2008).

The affect aspect during MI was not tested directly to gait. A few fmri studies have revealed that common neural networks are activated during the observation and imitation of an emotion. For example, Carr et al showed similar patterns of brain activation that include the insula and the amygdala while simply observe different facial expressions (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003). However, emotions are complex phenomena that can be related to MI in many different ways.

Subcortical structures were also linked to MI. Those structures include the cerebellum and the basal ganglia that play roles in motor planning and motor execution. The specific areas of the cerebellum active during movement execution are not the same as those active in MI. During MI activation of the upper parts of the posterior cerebellum that are linked to SMA, and premotor cortex has been occurred (Holmes & Calmels, 2008) (Hetu et al., 2013). The basal ganglia influence wide areas in the cortex, including pre-SMA, SMA, and dorsal prefrontal cortex which have been related to MI. Neural networks shared by the basal ganglia and the striato-thalamo-cortico-striatal pathways were shown to be activated during imagined movement (Munzert, Zentgraf, Stark, & Vaitl, 2008; Szameitat, Shen, & Sterr, 2007). According to these evidences it seems that subcortical regions also play role in the complex neural network related to MI. These findings raise important question regarding the ability of persons with PD to perform MI.

Number of studies examines the ability of patients to engage and practice motor tasks via imagery (Tamir, Dickstein, & Huberman, 2007). The most common findings were the prevalence of bradykinesia and inaccuracies in the generation of MI of self-body movements (Braun, Beurskens, Kleynen, Schols, & Wade, 2011; Heremans et al., 2011; Tamir et al., 2007). Thus, the disorder in imagery was found to parallel the actual deficit in movement generation. Studies focusing on differences in brain function between healthy subjects and patients during MI are scarce and mainly focused on upper extremity. Overall, activation of pre-SMA, SMA, DLPFC, and anterior cingulate area were repeatedly documented. These differences between healthy and PD subjects in MI must be taken into consideration when examining neural mechanisms of gait using MI.

In the recent years MI of gait in persons with PD has been used as an assessment tool to investigate freezing of gait (FOG) and as an intervention method to improve gait abilities. Two studies that used MI as an assessment tool used a similar paradigm of walking through doorways in different width and length. In these studies chronometric tests have been used to compare between time to complete real walking and imaginary walking. However, the results of these two studies were contradictory. Snijders et al. (Snijders et al., 2011) found an association between actual and imagined walking times in all groups while Cohen et al. (Cohen, Chao, Nutt, & Horak, 2011) demonstrated longer duration of imagined walking in patients with FOG as compared to patients without FOG. It is possible that these discrepancies in the chronometry tests

relate to differences in perceptual properties of the path width, and differences in position (supine vs. standing) and visual inputs (eyes open vs. close) during the performance of MI. Another potential explanation is the differences in the instructions given for MI.

Two studies that used MI as an intervention method also show that persons with PD can perform MI. Braun et al which compared MI practice to relaxation didn't find any differences in mobility improvement between these two methods (Braun et al., 2011). However, Tamir et al demonstrate that MI practice that was combined with real execution improve mobility more than conventional treatment (Tamir et al., 2007). Based on these current studies, the presence of disorders in imagery capacity does not justify reluctant to use MI of gait to investigate neural mechanisms in persons with PD. However, the ability of a patient with PD to perform MI must be evaluated before choosing this method and results should be interpreted carefully.

MI validation in older adults has been discussed in the literature according to three dimensions of MI: (1) vividness of motor representation, (2) temporal characteristics of the stimulated movements, and (3) accuracy of MI (Malouin et al., 2007; Mulder, Hochstenbach, van Heuvelen, & den Otter, 2007). Studies that used different imagery questionnaires as the Kinesthetic and visual imagery questionnaire (KVIQ) (Malouin et al., 2007) to assess MI vividness demonstrated that visual imagery would be preferable than kinesthetic imagery when performing MI of gait. Studies that examined the ability to reproduce temporal

characteristics of movements during MI showed that in older adults this ability is preserved for simple and usual movements but may be altered for unusual and constrained movements (Personnier, Paizis, Ballay, & Papaxanthis, 2008; Personnier, Kubicki, Laroche, & Papaxanthis, 2010; Skoura, Papaxanthis, Vinter, & Pozzo, 2005; Skoura, Personnier, Vinter, Pozzo, & Papaxanthis, 2008). In addition, it was shown that external cues, mostly visual and internal cues, mostly postural, may help older adults to increase the temporal congruence between simulated and executed movements (Personnier et al., 2008; Personnier et al., 2010; Skoura et al., 2005; Skoura et al., 2008). Although gait is a complex task it is a usual movement in everyday life. As such, temporal characteristics of MI of gait can be enhanced using external visual cues. External visual cues as virtual reality will form the environment and provide optic flow that will enhance temporal components of gait and will allow us to compare temporal measurements of real walking to imaginary walking.

Lower accuracy of motor representation was shown in older adults as compared to young (Gabbard et al., 2011; Saimpont et al., 2010). The ability to reach an object placed in different spatial locations (Gabbard et al., 2011) and the ability to retrieve the correct sequence of images (Saimpont et al., 2010) were reduced in older adults. Although gait is considered a complex task it requires less accuracy of motor representation than reaching an object with the hand. However, the decreased ability to retrieve sequences of image may be even greater when performing MI of complex task as gait. It is possible that by providing



external visual cues as virtual reality we can enhance the accuracy of the retrieved sequences. Nonetheless, the accuracy of MI of gait in older adults may be compromised.

Age related changes during MI at the brain level had been demonstrated using fMRI. It was shown that during MI of movements older adults do recruit motor related brain regions that are known to be involved in mental representation of a movement. These regions include the premotor cortex, the SMA, subcortical structures as the cerebellum and basal ganglia, the inferior parietal cortex (IPL), the somatosensory and motion-sensitive visual cortices, and even M1 (Leonard & Tremblay, 2007; Nedelko et al., 2010; Zwergal et al., 2012). In addition, the activity in most of these areas was found to be more prominent in elderly than in young subjects, possibly reflecting the compensation mechanisms associated with age (Nedelko et al., 2010; Zwergal et al., 2012).

In summary, these results demonstrate that, with aging, MI ability is well preserved for simple movements but may be altered for difficult movements. Thus, MI of gait can be enhanced using external visual cueing. In addition, fMRI studies show that besides some age related changes in the neural basis of MI similar neural networks are activated during MI in older adults and healthy young. Although MI of gait should be interpreted very carefully, it can be used to investigate neural circuits related to gait (Saimpont et al., 2013).

### 2.5.3 Virtual Reality as a tool to enhance engagement in MI

One of the difficulties during MI is to control the content of the imaginary scene and maintain the participant engaged in the scene. One method that has been suggested to improve the engagement in MI is Virtual Reality (VR). Virtual reality is often used to describe a wide variety of applications commonly associated with immersive, highly visual, 3D environments. These applications present artificially generated sensory information, from vision and proprioception, to illustrate real world. It consists of virtual environment (VE) which describes the simulation of a visual 3D environment presented to the subject via a display system. In the VE the user can anticipate and react to features in the environment as if they were real.

As such, using VR technology will allow us to create various environments and constraints that provide adequate sensory information to illustrate everyday life environments. The virtual environment serves as a powerful material to build a unique topographical representation. It can be used to present richly complex environments to the participant and can elicit a substantial feeling of realness and agency on behalf of the individual immerse in such an artificial world (Adamovich, August, Merians, & Tunik, 2009). In addition, the use of VR promises that environments will be standardized across participants.

The ability to be immersed in VR scene relies primarily on the visual system, more specifically on optic flow. Optic flow refers to the pattern of apparent motion of different elements in a visual scene caused by the relative motion between an observer and the scene. Optic flow field that is

created when observer moves in a rich textured environment provides information about self-motion and can thus be used to navigate in the correct direction and in the correct walking speed.

Only a handful of studies have investigated the use of VR in association with gait in PD. The use of VR as an evaluation tool in PD has been shown only for cognitive and executive function assessments (Klinger, Chemin, Lebreton, & Marie, 2006). In these studies persons with PD demonstrated ability to learn new paradigms of movement, but at a slower pace and with more difficulties in movement corrections (Albani et al., 2002; Messier et al., 2007) compared to control participants. Davidsdottir et al. (Davidsdottir et al., 2008) examined the impact of optic flow and egocentric coordinates on navigation during walking in persons with PD. The results showed that parietal-mediated perception of visual space is affected in PD including perception of optic flow speed and egocentric midline coordinates. In addition, the walking assessment demonstrated that visual input affects veering which corresponds to the shifting of the egocentric midline rather than to abnormal perception of optic flow speed.

In additional study a VR system based on an obstacle navigation task has been developed. In this study twenty persons with PD walked on a treadmill, while wearing a safety harness, 3 times a week for 6 weeks. The virtual scene consisted of an outdoor environment of a boardwalk on which virtual obstacles were placed at random intervals. The patients were required to walk within this environment while negotiating obstacles

without stepping on them. After 6 weeks of training, comfortable gait speed significantly improved, as did stride length, gait variability, and over-ground obstacle negotiation. The DT cost became smaller and there was evidence of improved task planning and set shifting (Mirelman et al., 2011).

In conclusion, VR can be used as a method to investigate gait in older adults and persons with PD. As demonstrated, MI which presents an internal stimulator and VR which present an external stimulator can be used to assess gait in fMRI in healthy elderly and persons with PD.

#### 2.5.4 MI and VR paradigm to assess complex motor tasks related to gait in fMRI

Two studies were found to use MI and VR paradigm to assess neural activation related to gait in persons with PD in MRI. In both studies the motor impairment that was investigated was freezing of gait (FOG). This is perhaps due to the unique susceptibility of FOG to cognitive, emotional and sensory stimulation that can be easily manipulated using both VR and MI and is more challenging over-ground. This is a specific example of the benefits of using MI and VR as tools for assessment allowing for exposing individuals to tasks that may be difficult to safely in the real world.

Snijders et al assessed differences in neural activation while manipulating the path width and length in which patients were asked to imagine themselves walking through (Snijders et al., 2011). The virtual environment (VE) presented to the subjects included a picture of a path with a target placed on it. The subjects were asked to observe the picture

and then close their eyes and imagine they are walking to the target. In this paradigm the environment was internally created based on the picture seen few seconds before. The duration of each imaginary walk was few seconds and it was analyzed base on event-related approach. While this study used a simple VE to form a more constructed MI, Shine et al used a complex VE that consisted of a straight corridor interspersed with environmental features, such as narrow doorways. The VE was displayed within the MRI scanner while their feet rested on a pair of MRI compatible foot pedals. Navigation within the VE was accomplished by alternate depression of left and right foot pedals. In this paradigm MI of walking involved alternating movements of feet while looking at the VE presented on the screen. The patients perceived themselves moving forward in the VE while having the possibility to stop or continue moving forward.

Two recent studies used fMRI to investigate neural activation while performing MI of complex movements related to gait. Wai et al.(Wai et al., 2012) included three groups of subjects: (1) persons with PD, (2) healthy elderly adults, and (3) healthy young, that were asked to imagine three tasks; walking initiation, stepping over obstacle and walking termination while watching a video clip that showed an actor executing these tasks. The results demonstrated no changes in activation between groups when performing the imagery task of gait initiation. In contrast, differences between groups were found during stepping over an obstacle and gait termination. During imagery stepping over an obstacle it was shown that similar networks of visual-motor coordination were activated in all three

groups. However, patients required more visual information and spatial details from bilateral MT/V5, precuneus, posterior parietal lobe and dorsal premotor area when presented with an obstacle. In the imaginary task of gait termination it was shown that different brain areas are activated in young healthy compared to elderly and patients. Young healthy participants showed increased activation in right inferior frontal gyrus and pre-SMA, while elderly and PD showed increased activation in bilateral MT/V5, right precuneus and cuneus. It was suggested that activation in these areas contribute to the process of visual-motor adaptation.

The second study by Peterson et al. (Peterson et al., 2013) examined neural mechanisms related to MI of five over-ground tasks in two groups of subjects; older adults and persons with PD. The tasks included forward and backward walking, turn to the right and left and quite standing. The three main findings of this study were: (1) across gait tasks, persons with PD showed reduced activation in the left GP compared to healthy subjects, (2) persons with PD showed increased activation in SMA during imagine turning compare to forward and backward walks, and (3) actual over-ground walking speed correlated with activation during imagined walking in several locomotion regions in persons with PD and not in older adults. These two studies are the only studies found to investigate neural mechanisms during imagined complex tasks related to gait. Therefore, the results of these studies will be used to form specific hypothesis regarding brain areas activated during imagined walking in complex environment.

Although these different paradigms of combined MI and VR seems to provide insight into the neural mechanisms related to gait, by definition these paradigms are still limited. This indirect investigation is unable to measure important variables in the production of locomotion, such as components of equilibrium, coordination, and synergism of different muscles groups while coping with gravity. Moreover, these paradigms do not contain weight-bearing, which is an essential component that facilitates spinal reflexes and the central pattern generator, utilizing the extensor loading response in the up- right vertical position (Dietz & Duysens, 2000; Dietz & Fouad, 2013). In the recent years a number of studies used functional Near Infra-red Spectroscopy (fNIRS) to measure neural activation while performing actual walking (Doi et al., 2013; Holtzer et al., 2011). As such, fNIRS can be used as a supplementary neuroimaging assessment to the fMRI in order to gain insight into the neural activation during actual walking.

#### 2.5.5 Neuroimaging of walking using fNIRS

fNIRS relies on optical techniques to detect changes in the hemodynamic response within the cortex when sensory, motor, or cognitive activation occurs. fNIRS detects brain responses in a manner similar to that of PET and fMRI. That is, increases in metabolic demand as a consequence of cognitive activation leads to the well-known hemodynamic response, which ultimately increases total blood flow, regional blood volume, and regional blood oxygenation (Arenth, Ricker, &

Schultheis, 2007). Like fMRI, fNIRS also depends on the ratio of oxy-Hb ( $\text{HbO}_2$ ) and deoxy-Hb (HHb), but in fNIRS the  $\text{HbO}_2$  and HHb are the primary light-absorbing constituents in the brain, and each absorbs near-infrared light in a different manner. To capture data regarding changes in the  $\text{HbO}_2$  and HHb ratio, the fNIRS procedure involves the placement of light sources and detectors on the scalp.

Near infrared light is projected through the scalp and skull, and ultimately penetrates into the first several millimeters of brain tissue. An array of photodiode detectors records the wavelengths of light reflected and absorbed. As motor and cognitive regions of the cortex for example, premotor cortex (PMC) and prefrontal cortex (PFC) are located in close proximity to scalp tissues, they are accessible to optical measurements (Leff et al., 2011). Therefore, fNIRS is an effective, indirect, optical neuroimaging method that monitors the hemodynamic response to brain activation, on the basis that neuronal activation and vascular response are tightly coupled (Franchignoni, Horak, Godi, Nardone, & Giordano, 2010; Toichi et al., 2004)

Over the last decade different movements have been used to investigate the fNIRS response to brain activation (Ishizu, Noguchi, Ito, Ayabe, & Kojima, 2009; Sato et al., 2007) in order to determine if the pattern of response was predictable based on neurovascular coupling. Despite different types of movements and protocols similar changes in hemoglobin were observed. Broadly, the hemodynamic response consists of a rapid increase in  $\text{HbO}_2$  and a slower, lower amplitude decrease in



HHb, which is proportionate with a change in regional cerebral blood flow (rCBF) (Leff et al., 2011). The temporal dynamics of the cortical hemodynamic responses show that the delayed response pattern (>2sec) consists of (1) rapid increase in HbO<sub>2</sub> and total hemoglobin (HbT) concentrations and (2) subsequent slower and smaller decrease in HHb concentrations (Akiyama, Ohira, Kawase, & Kato, 2006; Miyai et al., 2001; Sato et al., 2007).

All types of hemoglobin typically return to baseline some seconds after the motor stimulus ceases. Temporal data regarding recovery of cortical hemodynamics are rarely reported. However, those that are reported demonstrate that HbO<sub>2</sub> and HHb return to baseline approximately 9-10 sec after a brief motor stimulus ceases (Boden et al., 2007). The general lack of reporting makes it challenging to determine proper durations of motor rest between trials in experimental designs but from the data available, 10-15 sec of rest should be sufficient for short stimulation protocols.

Additional components related to the temporal hemodynamic response are time to peak (TTP) for HbO<sub>2</sub> and time to nadir (TTN) (lowest point) for HHb. In general it appears that HbO<sub>2</sub> get to peak within 5-10 s following onset of motor stimulation whilst HHb may be more variable. However, the temporal response as inferred from TTP and TTN are not fixed or predictable and is actually highly dependent upon the chromophore (the part of a molecule responsible for its color), type of motor stimulation, duration of onset and offset of stimulation, and length of

motor rest. Specifically, as the duration of motor stimulation increases so too does the TTP and TTN in cortical hemodynamics (Akiyama et al., 2006; Boden et al., 2007). In addition, response localization appears to be chromophore dependent. Specifically, HHb response has been shown to be more spatially localized, whereas HbO<sub>2</sub> is more generalized with typical responses being observed in almost all NIR channels (Leff et al., 2011; Miyai et al., 2001; Sato et al., 2007).

The fNIRS devices varied in number of electrodes and distance between transmitter and detector in each electrode. These parameters determine the spatial resolution of the device. Therefore, specific information regarding the device used in this study will be provided in the method section 3.5.3.

#### 2.5.6 fNIRS to assess gait and cognition

With the advanced in technology and the development of portable systems the use of fNIRS to investigate gait increased in the recent years. The fNIRS systems allow to measure changes in hemodynamic responses during real execution of gait. Miyai et al demonstrated specific changes in HbO<sub>2</sub> concentration in the medial portion of the primary sensorimotor regions and supplementary motor areas during gait (Miyai et al., 2001). In addition, these changes in HbO<sub>2</sub> concentration were shown to occur few seconds after the movement onset. However, this time from movement onset to change in HbO<sub>2</sub> depends both on task and cortical region. For

example, the time to HbO<sub>2</sub> change during gait is shorter than during arm swing (Miyai et al., 2001). In contrast, changes in HHb concentration occur in smaller areas of the brain and were shown to be minimal.

These findings demonstrate that in optical measurement HbO<sub>2</sub> is the most sensitive parameter of activity dependent changes in rCBF (Hoshi, Kobayashi, & Tamura, 2001; Miyai et al., 2001). In addition, it was shown that different tasks elicit different direction of changes in HHb; a decrease, no change or an increase. These inconsistent changes can be explained by the fact that changes in HHb depends on venous blood oxygenation and changes in diameters of arteries and venules (Hoshi et al., 2001; Miyai et al., 2001). These changes in vessels diameter effect light absorption which in turn change the received signal. When the blood vessel diameter exceeds 1mm the light will be absorbed completely and no signal will be recorded. Therefore only HbO<sub>2</sub> concentrations will be analyzed.

The cognitive components of walking in complex situations mainly those related to executive function play a major role in the ability to perform different walking tasks. The fNIRS method will enable us to explore frontal brain activation related to walking in complex environment. In the early 1990s, Villringer et al introduced fNIRS as a “new tool” for studying hemodynamic changes in the brain during cognitive activities (Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993). They found a pattern of increases in HbO<sub>2</sub> and corresponding decreases in HHb associated with cognitive tasks that were not due to alterations in skin

blood flow, but rather due to hemodynamic changes in the brain. However, as compared to studies of motor and visual tasks, fNIR findings of cognitive functions are more complex and varied, with less consistency in hemodynamic response patterns of HbO<sub>2</sub> and HHb (Arenth et al., 2007).

In the recent two decades the use of fNIRS to investigate cognitive function increased. However, methodological differences between studies limit our ability to come up with more specific conclusions regarding hemodynamic patterns during cognitive tasks (Arenth et al., 2007). Schroeter et al measured changes in HbO<sub>2</sub>, HHb and THb during the Stroop test in 14 healthy subjects (Schroeter, Zysset, Kupka, Kruggel, & Yves von, 2002). They found patterns of increased HbO<sub>2</sub> and THb, and decreased HHb concentrations that were greater in the lateral prefrontal cortex bilaterally for contrasting trials as compared to natural or matching trials. This finding suggests that the interference during contrasting trials induced stronger brain activation (Schroeter et al., 2002). Another study investigated changes in hemodynamic response while performing single attention versus higher cognitive processing tasks with 20 healthy adults (Toichi et al., 2004). The results demonstrated increases in HbO<sub>2</sub> and decreases in HHb in the prefrontal cortex during high level cognitive tasks (Toichi et al., 2004).

#### 2.5.7 fNIRS in healthy elderly and persons with PD

Only one study investigated gait in older adults using the fNIRS device (Holtzer et al., 2011). This study aimed to evaluate whether

increased activations in the prefrontal cortex (PFC) were detected in dual task that include walking while talking compared with normal walking in 11 young and 11 elderly participants. The results demonstrate a robust bilateral increase in activation in the pre frontal cortex during the dual task walking compared with normal walking. Furthermore, it was demonstrated that healthy elderly demonstrate a smaller increase in HbO<sub>2</sub> levels during the dual task compared to healthy young. The authors' conclusion was that frontal lobe activation during the dual task is modified by age suggesting that older adults may under-utilize the PFC in attention-demanding locomotion tasks (Holtzer et al., 2011). These findings contradict some of the fMRI literature in which increased activation during dual task in older adults was related to compensatory mechanism. Technically both fMRI and fNIRS relay on BOLD signal and similar patterns of change would be expected.

Only two studies that looked at fNIRS in relation to PD were found in the literature (Murata et al., 2000). The first study investigated changes in cerebral blood oxygenation (CBO) in the frontal lobe induced by direct deep brain stimulation of the Thalamus or Globus Pallidus. The study results indicate that under conditions of neural activation in the frontal lobe, HbO<sub>2</sub> increases in all participants while changes in HHb differ between subjects (Murata et al., 2000). This finding is in accordance with the literature in which HHb changes are more difficult to measure and more controversial compared to HbO<sub>2</sub> which is more robust (Obrig & Villringer, 2003). The second study assessed changes in HbO<sub>2</sub> in the

frontal lobe during freezing of gait. Increased level of HbO<sub>2</sub> was found just before and during episodes of freezing of gait that occurred during anticipated turns, a task that requires motor planning (Maidan et al., 2015). This study demonstrates the feasibility of measuring frontal activation during real walking in persons with PD.

To date, there have been few clinical studies that have employed fNIRS. This may relate to the fact that fNIRS is still new compared to other imaging technologies. Also the research published to date is relatively conservative, focusing on establishing the validity and reliability of fNIRS, which limits its clinical application. The evidence from this literature review supports the assumption that fNIRS technology can be used to evaluate neural underpinnings of cognitive components of gait during actual walking. The fNIRS evaluation during real walking will be supplementary to the MI of walking performed in the MRI scan. Measuring frontal lobe activation during real walking in a complex situations will provide us a window into the mechanisms of executive function in the performance of this task.

#### 2.5.8 fNIRS and fMRI as supplementary methods

The use of fNIRS and fMRI simultaneously was made for two purposes: (1) validate the fNIRS as possible method to examine neural activation during performance of cognitive paradigms (Cui, Bray, Bryant, Glover, & Reiss, 2011; Heinzel et al., 2013) and (2) develop techniques for connecting hemodynamic fNIRS temporal signal and hemodynamic fMRI

spatial information to create high resolution spatiotemporal maps of the brain (Heinzel et al., 2013; Yuan & Ye, 2013). Comparison between fNIRS and fMRI measurements while performing different cognitive tasks demonstrated similar pattern of frontal brain activation (Cui et al., 2011; Heinzel et al., 2013). Cui et al conducted a battery of cognitive tasks to measure activation of multiple brain regions using fNIRS and fMRI (Cui et al., 2011). The tasks included finger tapping, a go/no go task, a judgment of line orientation task, and a visuo-spatial N back working memory task. These tasks require response inhibition, working memory, and visuo-spatial skills strongly associated with frontal brain activation. It was found that, while many channels showed strong correlations between BOLD and HbO<sub>2</sub> and HHb, there was a wide range in the correlation values. Several factors were found to be responsible for the wide range, including scalp-brain distance and Contrast to noise ratio (CNR). The cognitive task was not found to be responsible for this wide range in the correlations (Cui et al., 2011).

Similar results were demonstrated by Heinzel et al while performing the intertemporal choice (ITC) paradigm, a complex cognitive task in which different reward options are offered and tested (Heinzel et al., 2013). In this study better correlations were demonstrated for HbO<sub>2</sub> than for HHb. Although these results are encouraging they involve only the performance of cognitive tests. Number of studies that involved motor performance included only a simple task of finger tapping. These studies showed a very good correlation between fMRI and fNIRS however, mixed

conclusions were found for HbO<sub>2</sub> and HHb (Heinzel et al., 2013; Yuan & Ye, 2013). Although these studies showed promising results we should keep in mind that they involved a simple motor task and included young healthy participants.

Overall, a good agreement was found between the results of fNIRS and fMRI. However, the fNIRS measurements in the fMRI scanner might differ from common fNIRS measurements. In the presented studies the participants were in a supine position during the fNIRS–fMRI measurements. As such systemic physiological parameters might differ from tests conducted while participants were in a sitting position (Tachtsidis et al., 2004). These studies validate the hemodynamics responses received from fNIRS located on frontal brain areas. However, in this proposed study the combined use of fNIRS and fMRI aim to extend the fMRI results obtained from motor imagery of gait into real execution of gait using the fNIRS. These two neuroimaging methods will be used to measure frontal brain activation during similar paradigms that are considered to activate neural circuits related to gait. In this proposed study these two methods; fMRI and fNIRS will not be performed simultaneously as in these studies presented.



### 3 METHODS AND PROCEDURES

#### 3.1 Research design

The study will use a cross sectional design. Two groups of subjects will be included; healthy older adults and persons with PD. A repeated measures design (condition x group) will be used with two levels; within group and between groups. Walking conditions will be performed while being monitored with the fNIRS and imagined walking will be assessed in the MR scanner.

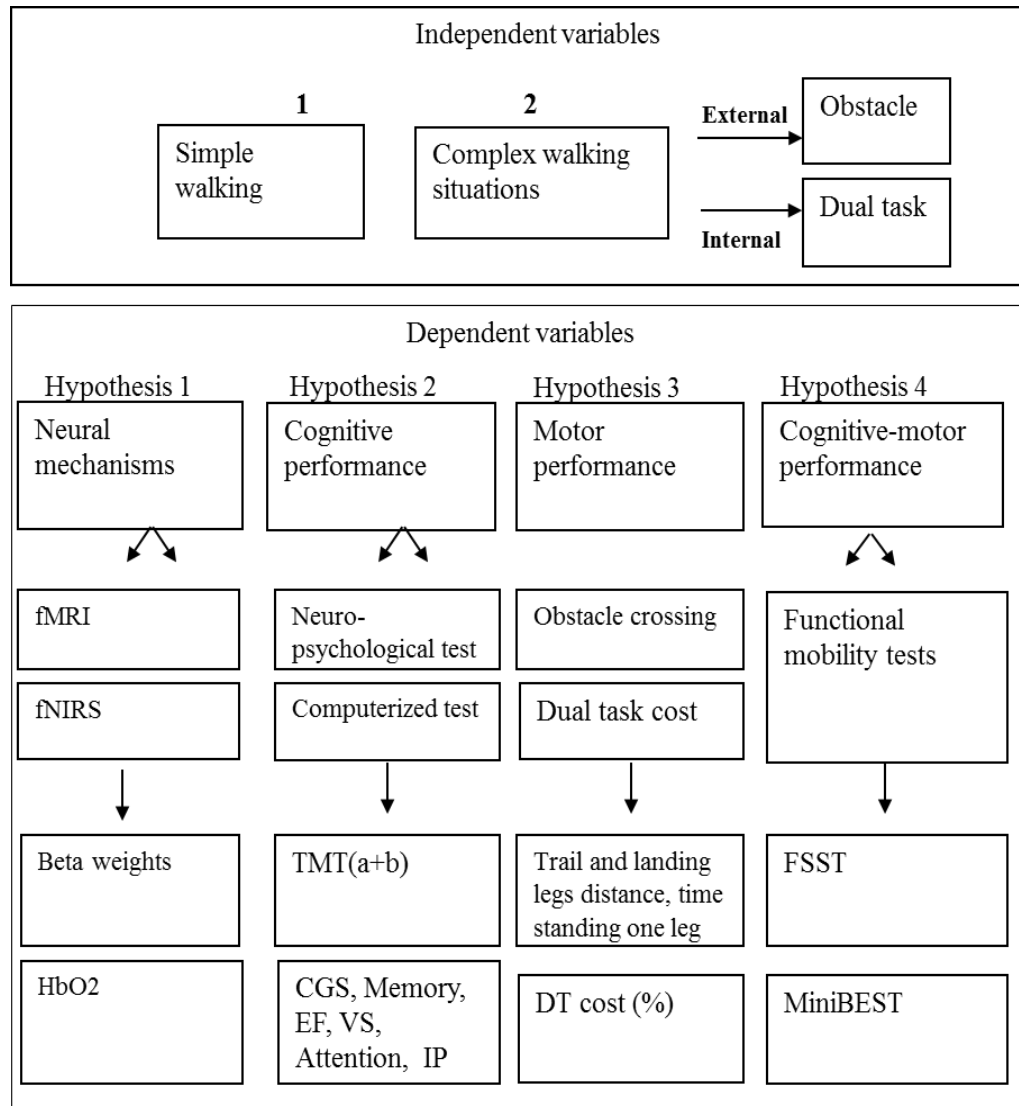
#### 3.2 Variables

To define the cohort different characteristic measures will be collected. These will include: age, gender, weight, height, and leg length. Additional measures for persons with PD will include: disease duration and Unified Parkinson Disease Rating Scale (UPDRS).

This multifactorial design will include two independent variables, seven primary dependent variables, and five secondary dependent variables. The following is the description of the variables collected.

The independent variables consist of two walking conditions; (1) simple walking that includes walking in a straight clear path and (2) complex walking which will encompass two different components of complexity; (a) negotiating obstacles and (b) dual tasking (Figure 2).

Figure 2 below presents the different variables included in the study.



**Figure 2:** The independent and dependent variables as refer to each hypothesis

The dependent variables will be described as they relate to each hypothesis.

### 3.2.1 Hypothesis 1 (neural mechanisms of walking in complex situations)

#### Primary variables (Table 1)

1. fMRI: Beta weights for two contrasts (a) obstacle path vs. clear path (b) navigation vs. straight path. It will be obtained from (a) obstacle walking paradigm and (b) navigation paradigm. The beta-weight variables are measures of brain activation that allow us to define the specific activated areas and quantify their level of activity. A large positive beta weight for each contrast will indicate more activation during the complex walking condition. The paradigms will be described in section 3.6.4.
2. fNIRS: HbO<sub>2</sub> concentration ( $\mu\text{M}$ ) during obstacle course, dual task and straight line walking conditions. HbO<sub>2</sub> level will be used to measure frontal lobe activation during these different walking conditions. Comparison between the conditions will indicate which condition elicits higher frontal lobe activation. The different walking conditions will be described in detail in section 3.6.3.

#### Secondary variables (Table 2)

1. fMRI: Beta weights for the contrast motor imagery of walking vs. watching the same scene without imagined walking. It will be conducted for each of the imagined walking conditions; usual walking, walking while negotiating obstacles, walking while navigating. A large positive beta weight will indicate more activation during imagined walking than watching alone. The watching paradigm will be described in detail in section 3.6.4.

2. fNIRS: HbO<sub>2</sub> concentration (μM) during standing while serially subtracting 3s and walking while counting forward. Comparison between all conditions will indicate which condition requires higher level of frontal lobe activation.

### 3.2.2 Hypothesis 2 (cognitive performance and neural mechanisms)

Primary variables (Table 1)

1. The scores that will be obtained from the computerized tests. These will include: global score (CGS), executive function score, visual spatial score, attention score, memory score, and information processing scores. The computerized tests will be described in detail in section 3.6.2.

Secondary variables (Table 2):

1. Trail Making test (TMT). Represents a measure of attention, speed, and mental flexibility. It consists of two parts that are timed. Part A requires the individual to draw lines to connect 25 encircled numbers distributed on a page while part B is similar except the person must alternate between numbers and colors and is believed to take longer to complete. Test-retest reliability and content and construct validity have been shown for this test (Sanchez-Cubillo et al., 2009).

### 3.2.3 Hypothesis 3 (motor performance of complex situations and neural mechanisms)

Primary variables (Table 1) :

1. Obstacle negotiation: Trail leg and landing leg distance from the obstacle. These measurements will be obtained from a sensorized mat, PKMAS. The validity and reliability of the PKMAS for measuring spatio-temporal measurements was shown to be high for elderly and persons with PD ( $0.82 < ICC < 0.99$ ) (McDonough, Batavia, Chen, Kwon, & Ziai, 2001; Menz, Latt, Tiedemann, Mun San, & Lord, 2004; Webster, Wittwer, & Feller, 2005). The PKMAS system will be described in detail in section 3.5.2.
2. Dual task cost. It is defined as the percent change in performance relative to the single-task condition. DT cost will be calculated for gait measurements such as gait speed and stride length according to the equation:  $((\text{dual task} - \text{only walk}) / \text{only walk}) \times 100$ .

Secondary variable (Table 2):

1. Obstacle course: Duration of standing on one leg while stepping over an obstacle. It is defined as the time from which leading leg leave the mat to the time it contact the mat again. This variable will be obtained from the PKMAS mat.
2. Dual task performance: percent of successful subtractions  $(\text{correct subtractions} / \text{total subtractions}) \times 100$  divided by duration of walking task.

#### 3.2.4 Hypothesis 4 (mobility-function and complex walking performance)

Primary variables (Table 1) :

1. Four step square test (FSST). It is a dynamic balance test that was developed to assess the rapid change in direction while stepping forward, backward and sideways over a low obstacle. The score represent time to complete the task. Inter-rater and test-retest reliability were found to be high (ICC = .99 & .98 respectively)(Lewis, Martinez, & Rogers, 2005). Concurrent validity was found through significant correlations ( $p < .001$ ) with other balance measures such as the Step Test ( $r = -.83$ ), Timed Up and Go (TUG;  $r = .88$ ), and Functional Reach Test ( $r = -.47$ )(Lewis et al., 2005).
2. The Mini-BEST. It is a test of dynamic balance that specifically focuses on anticipatory transitions, postural responses, sensory orientation, and dynamic gait(Franchignoni et al., 2010). It includes 14 items in which each item is scored from (0–2); a score of 0 indicates that a person is unable to perform the task while a score of 2 is normal. The best score is the maximum amount of points, being 32. An excellent inter-rater (ICC  $\geq 0.91$ ), and test-retest (ICC  $\geq 0.88$ ) reliability have been shown for this test(Leddy, Crowner, & Earhart, 2011).

Tables 1 and 2 below summarize the primary and secondary variables of the study.

*Table 1 The primary variables of the study*

Hypothesis	Primary variable	Instrument	Measure	Purpose
1	Contrasts: (a) obstacle path vs. clear path (obstacle walk) (b) navigation vs. straight path (DT walk)	fMRI  Obstacle and navigation paradigms	Beta weights	Brain activation during walking in complex situations
	Changes between comfortable walk, obstacle walk, and DT walk	fNIRS  Gait performance	HbO <sub>2</sub> (μM)	Frontal lobe activation during walking in complex situations
2	GCS, executive function, visual-spatial, memory, info-processing, and attention	Computerized cognitive tests	Indices score of 6 cognitive domains	Cognitive performance
3	Trail and landing legs distance from obstacle	PKMAS	Distance in cm	Obstacle negotiation performance
	Dual task cost	PKMAS	Percent change in gait measurement	DT performance
4	FSST	4 sticks and stopwatch	Time to perform (cm)	Functional-mobility performance
	Mini-BEST	Stopwatch, shoe box, incline surface	Ordinal score	Functional-mobility performance

Table 2 *The secondary variables of the study*

Hypothesis	Primary variable	Instrument	Measure	Purpose
1	Contrast dual task vs. feet alone + subtracting 3s alone Changes between standing while serially subtracting 3s and walking while counting forward	fMRI Dual task paradigm fNIRS  Gait performance	Beta weights  HbO <sub>2</sub> (μM)	Strengthen the motor imagery paradigms Control conditions
2	TMT	Neuro-psychological tests	Time to complete in seconds	Cognitive performance
3	Duration of stepping over obstacle Total subtractions and number of errors	PKMAS  Walking while dual tasking	Time (sec)  Numbers (n)	Obstacle performance Performance of cognitive task



### 3.3 Subjects

A sample of convenience will be used. Healthy older adults and persons with PD who will express an interest in participating in the study will be offered enrollment if they meet inclusion criteria. Subjects will sign an informed consent prior to participating in the study.

Suitability for inclusion in this study will be determined according to the following criteria:

- Age between 60-90 years. Both men and women will be included
- MMSE  $\geq 24$
- Able to undergo the MRI (metal implements are MRI compatible and no claustrophobia is reported)
- No severe hearing or visual impairment
- No history of stroke, traumatic brain injury or other neurologic disorder
- Able to walk independently for 5 minutes
- No psychiatric disorder
- Able to comply with the whole protocol
- For PD: Diagnosis of PD meeting United Kingdom Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992) determined by a neurologist
- For PD: Hoehn and Yahr stages II-III (Hoehn & Yahr, 1967)

### 3.4 Sample size

The sample size estimate is based on extrapolations from a pilot study of 5 persons with PD conducted in our lab and one study from the literature (Yogev et al., 2005). The neural activation variables in our study will be obtained from the imaginary walking paradigm in the fMRI and changes in HbO<sub>2</sub> during different walking conditions with fNIRS. Effect size and Cohen's d for the contrast between imaginary straight walking and imaginary obstacle negotiation were calculated using the t test value and degrees of freedom for a between conditions t-test. For the fNIRS, and dual task cost variables effect size and Cohen's d were calculated for the difference in HbO<sub>2</sub> levels and swing time variability in a usual walking condition and walking while dual tasking using means and standard deviations of two groups; older adults and persons with PD.

As seen from table 3 the effect size differ between variables from the fMRI and variables from the fNIRS. This discrepancy is likely due to the robustness of the fMRI method as compared to the fNIRS. Using a one sample t-test analysis, with  $\alpha=0.05$  and power of 80%, a sample size of 13 persons with PD will be required to detect between group differences in the fMRI test while 22 subjects will be required to detect significant changes in the fNIRS test.

*Table 3 Effect size for primary variables*

	Cohen's d	Effect size r
Beta values of imagined walking paradigm	2.13	0.73
HbO <sub>2</sub> concentration	0.89	0.40

The study of Yogev et al. showed a difference of 1.53 in swing time variability between simple and dual task walking conditions in 30 persons with PD and 28 healthy older adults (Yogev et al., 2005). Based on this effect, 21 subjects will be needed to achieve 99% power. Aiming for statistical power of 80% reduces the sample size to 15 subjects in each group for measuring dual task cost of gait variables. Based on this assessment 15 subjects will be included in each group.

### 3.5 Instrumentation

#### 3.5.1 Neuroimaging

Two complementary neuroimaging systems will be used in this study in order to elucidate changes in brain activation during walking in complex situations. These two systems are the fMRI and the fNIRS. The fMRI will be used to underline neural mechanisms associated with complex walking however due to fMRI limitations it can be investigated only during imagined walking or alternate movements of feet in a supine position. On the other hand the fNIRS system will be used to measure frontal lobe activation related to complex walking during real walking performance.

##### 3.5.1.1 The fMRI system

Imaging will be performed on a GE 3T Signa HDxt scanner. All images will be acquired using a standard eight-channel head coil. For each subject a structural scan three-dimensional spoiled gradient (3D-SPGR) echo sequence will be collected: field of view (FOV) 250 x 250

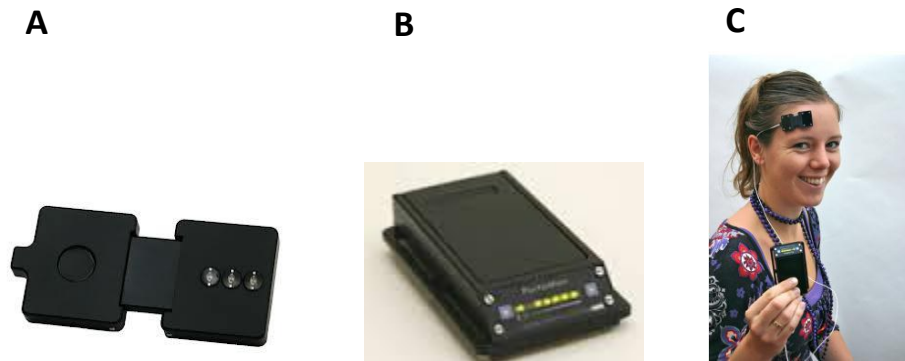
mm; matrix size 256 x 256; voxel size .98 x .98 x 1; Repetition Time (TR) 9 msec; Echo Time (TE) 3.6 msec. Functional images will be acquired using a single-shot echo-planar T2\*-weighted sequence with the following parameters: FOV 200 x 200 mm; matrix size 128 x 128; 39 slices with 3 mm thickness and no gap; TR/TE 3000/35 msec; flip angle 90°. Acquisition orientation obtained in the fourth ventricle plane.

The visual stimulus delivery and the response acquisition of the three tasks conducted in the scanner will be controlled using Presentation software (Neurobehavioral Systems, Albany, USA). Images will be projected via an LCD projector (NEC, VT660K) onto a screen positioned in front of the subjects' forehead and viewed through a tilted mirror. Responses will be gathered with an MRI-compatible response box that contained four buttons (HH-1 x 4L, Current Designs).

#### 3.5.1.2 The fNIRS system

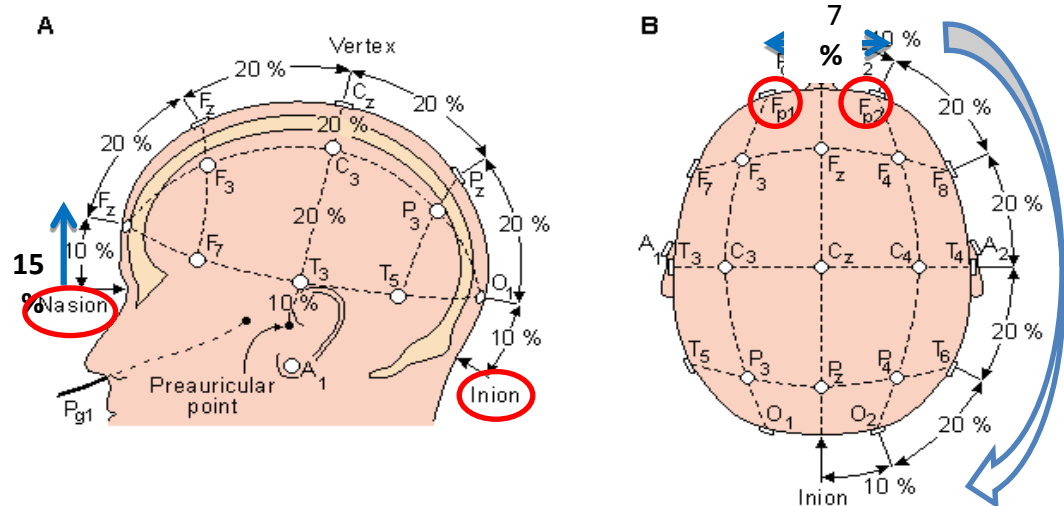
A wireless fNIRS system that consists of two separate pairs of near infrared probes to monitor absorption of light across the forehead (PortaLite, Artinis, The Netherlands) will be used in this study (Figure 3). One NIR emitter and detector pair will be placed over the left frontal cortex region of the forehead, while the second emitter and detector pair will be placed over the right frontal cortex region of the forehead. The exact location of the probes will be according to point Fp1 and Fp2 in the EEG maps (Figure 4). These points are at height of 15% from nasion to nasal distance and at width of 7% of head circumference to left and right from the middle line.

The probe is small and easy to attach. It will be attached to the skin using double-sided sticker and covered with a black cloth to prevent penetration of light. Data will be recorded continuously at 10 Hz, from the beginning of the rest period to the end of the trial.



**Figure 3:** fNIRS device

(A) The portaLite probe which contain the transmitter and the detector, (B) The Portimon that hold the battery, and (C) The location of the probe on right forehead.



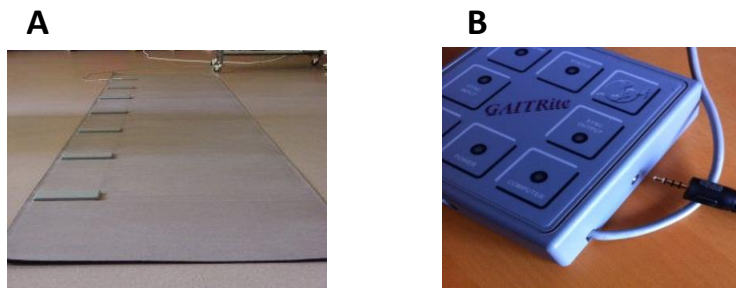
**Figure 4:** Probe location according to EEG maps.

(A) represent the height of the probe 15% of nasion to inion and (B) represent the width of the probe 7% of head circumference to right and

left. Figure from the webversion of the book by Jaakko Malmivuo & Robert Plonsey: *Bioelectromagnetism - Principles and Applications of Bioelectric and Biomagnetic Fields*, Oxford University Press, New York, 1995", chapter 13.3.

### 3.5.2 Gait

The PKMAS system is a sensorized 7 meter carpet (Zeno Walkway, PA, USA) that captured individual footfall data using embedded pressure sensors. The system includes the PKMAS walkway (Figure 5A) and platinum interface (Figure 5B). The PKMAS walkway contains sensor pads encapsulated in a roll up carpet to produce an active area variable with the actual length of the carpet. The PKMAS platinum interface supplies power to the PKMAS walkway, provides the communications cabling between the PKMAS walkway and the host Personal Computer (PC), and provides the interface and synchronization with external system.



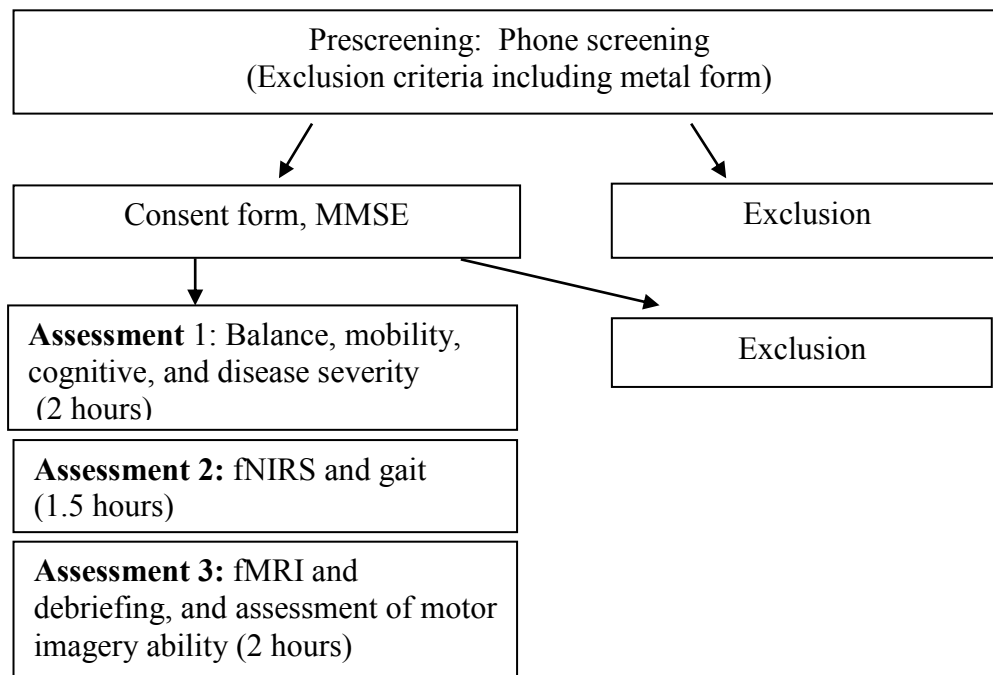
**Figure 5:** PKMAS mat

(A) walkway and (B) Platinum Interface

## 3.6 Research Protocol

The study will be conducted in the laboratory of gait and neurodynamics in Tel Aviv Sourasky medical center. The subjects will be invited to the lab for three separate assessments within a week. All

assessments will be conducted during the ON state, approximately 1 hour after last medication. The first assessment will include motor, cognitive and disease severity evaluation. The motor evaluation will include balance and mobility tests, the cognitive evaluation will include computerized and pen and paper tests, and the disease severity will consist of the UPDRS. The second assessment will include fNIRS and gait tests, and the third assessment will include fMRI scan and evaluation of motor imagery ability.



**Figure 6:** Study's protocol

A schematic outlining of the study is presented below (Figure 6).

### 3.6.1 Pre-screening and screening

Before subjects will be invited to the lab they will undergo a phone screening to determine eligibility to participate in the study. The phone

screening will include questions referring to the study's exclusion criteria as subject's age and questions from the metal form of MRI. The metal form includes questions as the existence of pace-maker or any other incompatible MRI metal objects. Subjects that will be found eligible will be scheduled for screening and first assessment. Screening will include the inform consent and the MMSE. After signing the inform consent subjects will perform the MMSE, and only those who will score equal or higher than 24 will be included in the study.

### 3.6.2 First assessment

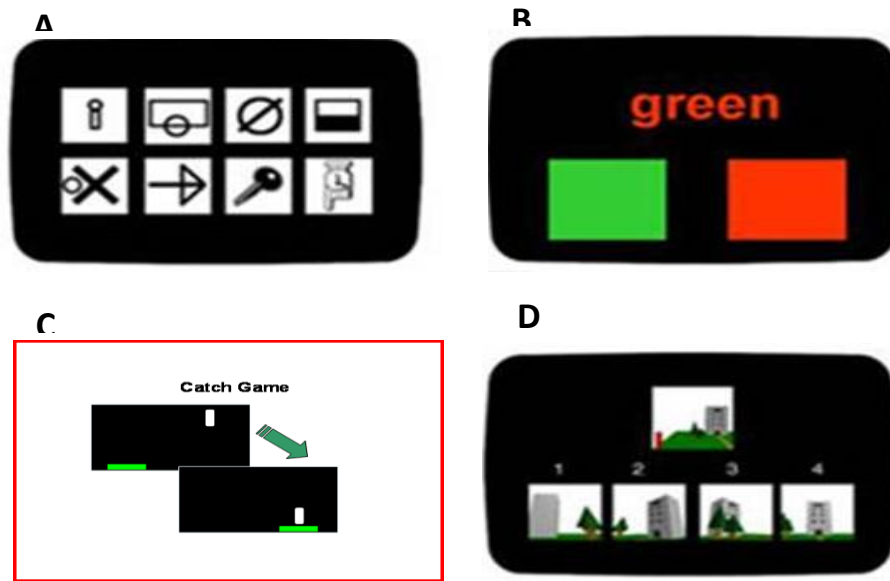
#### 3.6.2.1 Balance, mobility and cognitive tests

Balance and mobility will be assessed first using the FSST test and the Mini-BEST test. The FSST duration is five minutes and the Mini-BEST duration is 20 minutes. The cognitive tests will be performed next, first the TMTa and TMTb and then the computerized neuropsychological test battery (Mindstreams; NeuroTrax NeuroTrax Corp, Newark, NJ). The TMT duration is between 2-6 minutes and the computerized test duration range between 30-45 minutes depends on the subject's performance.

The battery will include six tests: (1) Go-NoGo response inhibition- a reaction time test in which green squares are presented at pseudo-random intervals, and the subject must press the mouse button as quickly as possible whenever a square appears, (2) Non-verbal memory- subject is presented with multiple pictures of common objects followed by immediate recognition test. A delayed recognition test for these same



objects is administered following a delay of approximately 5 minutes (Figure 7), (3) Stroop test- the task is composed of two conditions: congruent in which words appeared in their matching colors and incongruent whereas colors did not match their content. Patients are required to indicate the color of the ink while disregarding the meaning of the word presented (Figure 7), (4) Catch game- patients need to “catch” the white object falling vertically from the top of the screen (Figure 7), (5) visual spatial processing- in a common scene a cue is given to indicate the perspective from which the scene should be view (Figure 7), (6) Staged information processing- measures information processing at increasing levels of complexity. The test is comprised of 3 levels of information processing load: single digits, two-digits and three digits arithmetic problems that are presented at three different rates. Based on these tests the Neurotrax software composites indices of six cognitive domains on an IQ-like scale, with 100 representing the estimated population mean normalized for age and education. The domains include: (1) global cognitive score, (2) memory, (3) executive function, (4) visual spatial, (5) attention, and (6) information processing.



**Figure 7:** Neurotrax tests

(A) Non-verbal memory, (B) Stroop-color test, (C) Catch game and (D) Visual spatial

### 3.6.2.2 Disease severity and classification

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used rating scale in the clinical study of PD. Mainly used to follow the longitudinal course of PD. It consists of four parts: Part I: non-motor experiences of daily living, Part II: motor experiences of daily living, Part III: motor examination and part IV: motor complications. Part I has two components: one is assessed by the investigator with all pertinent information from patients and caregivers, and the other is completed by the patient with or without the aid of the caregiver, but independently of the investigator. Part II is a self-administered questionnaire but can be reviewed by the investigator to ensure completeness and clarity. Part III is completed by the rater and has instructions for the rater to give or

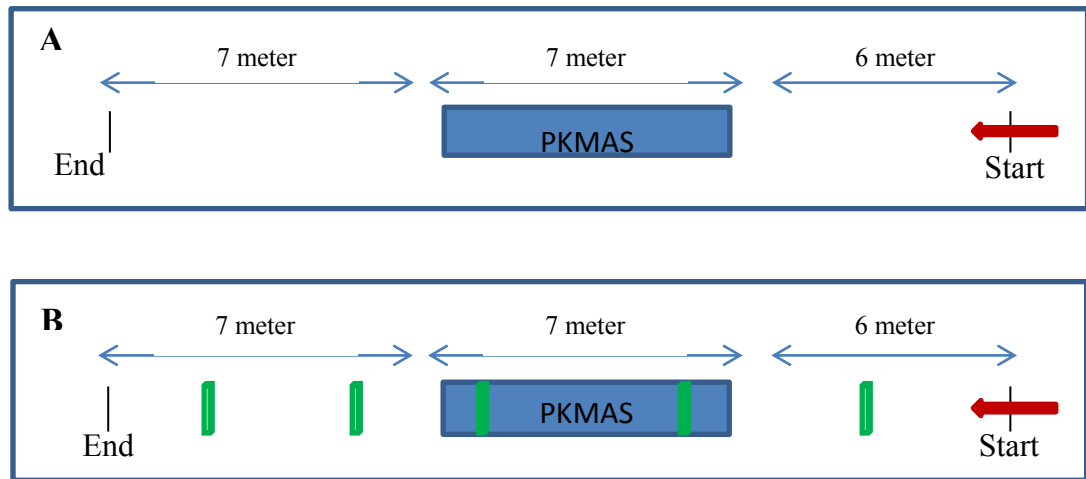
demonstrate to the patient. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater. The administration of the UPDRS takes approximately 20 minutes.

### 3.6.3 Second assessment

#### 3.6.3.1 Gait and fNIRS test

The gait test will be performed with the fNIRS system in a 20 meter corridor. It will consist of five conditions (four walks and one standing) that will be separated with 2 minutes of rest while sitting on a chair. After each rest 30 seconds of quiet standing will be performed as base line. The four walking conditions will include: (1) usual walk in which patients will be asked to walk at their comfortable speed, (2) dual task walk in which patients will be asked to walk at their comfortable speed while subtracting 3, (3) obstacle course walk in which patients will be asked to walk at their comfortable speed while stepping over five obstacles (shoe boxes) placed on the course, and (4) counting walk in which patients will be asked to walk at their comfortable speed while counting forward starting from one (Figure 8). The counting condition was added to control for facial movements and verbalization of words while walking. Each condition will be performed 5 times, in each time the subject will stand for 20 seconds, walk for 20 meters or 30 seconds, stand in place for 20 seconds and perform 180° turn. Spatio-temporal measurements of gait will be measured from the PKMAS placed 6 meters from the starting line. The standing

condition will include quite standing for 20 seconds and serially 3 subtractions for 30 seconds in order to examine frontal lobe activation



during simple cognitive task. Five repetitions will be performed.

**Figure 8:** The setting of the fNIRS walks

(A) The setting for straight and DT walks, (B) The setting for obstacle course walk.

### 3.6.4 Third assessment

#### 3.6.4.1 Motor Imagery ability

Two tests will be performed in order to estimate MI ability; the chronometric test and Kinesthetic and Visual Imaginary Questionnaire (KVIQ). The chronometric tests will be performed for normal and fast walking in a course of 10 meter long. Subjects will be asked to walk in their comfortable speed for 10 meters and then imagine they are walking this distance back. The imaginary walk will be performed with eyes open while looking at the end point. Both executed and imagined walk will be timed with a stopwatch. The same procedure will be performed for fast walking.

In addition, the KVIQ will be administrated in order to assess MI ability. The KVIQ assesses on a five-point ordinal scale the clarity of the image (visual: V subscale) and the intensity of the sensations (kinesthetic: K subscale) that the subjects are able to imagine from the first-person perspective.

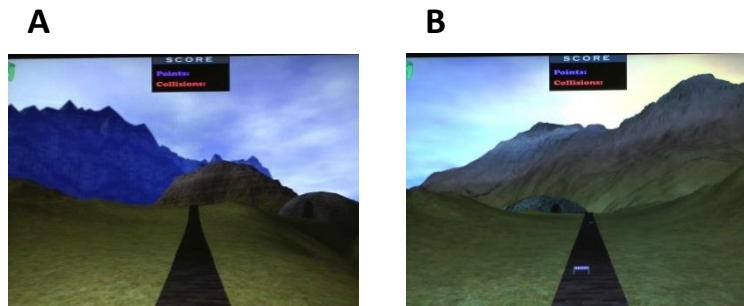
#### 3.6.4.2 fMRI scan

The subjects will fill out the metal form and sign it. The metal form includes questions to ensure subject's eligibility to the MRI scan. For example, questions regarding previous operations in which incompatible metal had been used. Before entering the scanner, subjects will undergo a familiarization and practice period. During this period, both virtual reality scenes (obstacle and navigation) will be shown and subjects will be asked to imagine themselves walking in these scenes. In addition, they will receive an example map and they will be asked to plan their route from starting point to end point. They will also be given a response box and will practice pressing on the buttons when reaching a bifurcation or when star appear on the screen. This practice period will last until subjects assert that they understand the tasks and are able to plan a correct route from starting point to end point.

The fMRI protocol will include 3D-SPGR anatomical sequence, and three tasks: (1) Obstacle task: imaginary walking in a path with and without obstacles, (2) Navigation task: imaginary walking in a straight or bifurcation path, and (3) Visual control task: watching a video that includes path with obstacles, without obstacle, and bifurcations.

**Obstacle task:** A movie of 9:45 min will be projected onto the screen. The first 45 seconds of the movie are a gray screen that serves as a baseline. After the baseline a virtual environment scene of a long path in a park landscape will be displayed. While the virtual park is displayed the subjects will be required to imagine they are walking in the presented scene. No movements of the legs will be allowed. The optic flow of the movie was calculated based on a normal walking speed of 1.2 m/s. The displayed movie includes two conditions: (1) clear path and (2) path with obstacles (Figure 9). Each condition last 45 seconds and is repeated four times, creating 8 alternating blocks. During the obstacle path the subjects will be asked to imagine they are walking and stepping over the obstacles.

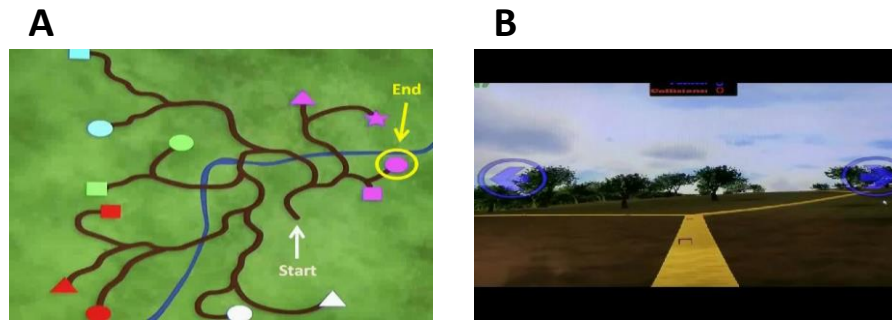
The subjects' awareness and attention to the virtual environment scene will be assessed during the entire task. In each block every 45 seconds a star will appear on the right or left side of the screen. Subjects will be asked to press on the right or left button of the response box when a star appears on the screen. For example, if the star appears on left side of screen the subject needs to press the left button. The purpose is to objectively assess the subject's awareness along the task.



**Figure 9:** The virtual park landscape

*The park landscape presented to the subjects in the MR scan. (A) Clear path, (B) Obstacle path*

**Navigation task:** A movie of 4:20 minutes will be presented to the subjects. The movie will consist of two navigation blocks each of 2:05 minutes, separated with 10 seconds periods of no stimuli (baseline). Each block will include; 45 seconds in which a map is presented and subject is required to plan a route from starting point to end point (Figure 10A), and 1:20 minutes during which the subject is required to imagine he is walking in the planned route (Figure 10B). Each route will include three bifurcations and subjects will be required to press on the right or left button when approaching a bifurcation based on the map shown at the beginning of each block (Figure 10A). This task possess a high cognitive load as subjects required to imagine themselves walking while memorizing the map and making decision about the direction they should turn in the bifurcation.



**Figure 10:** The navigation paradigm

*(A) The map on which subjects plan the imaginary walking route. According to this map the subject will need to turn right in the first bifurcation, right in the second bifurcation, and left in the third bifurcation (B) An example of bifurcation in which subjects need to decide if turn left or right.*

**Visual control task:** A video of 4:30 minutes will be presented to the subjects. The video will consist of three parts; (1) straight path with no obstacles, (2) straight path with obstacles, and (3) bifurcation path. The duration of each part will be thirty seconds and each will be repeated three times. The subjects will be instructed to watch the video without performing motor imagery of walking. This task will be the baseline condition and will allow us to determine which brain areas are associated specifically with motor imagery performance after removing / controlling for observation of the path.

After completing the fMRI protocol and taking out from the scanner subjects will be debriefed for their motor imagery performance and their ability to watch the video without imagine themselves walking. The purpose of the debriefing is to validate and evaluate the performance on these three paradigms. Table 4 below summarizes the three fMRI paradigms.



Table 4 *The fMRI paradigms*

Paradigm	Design	Duration	Purpose
Obstacle	Block design: clear path block, obstacle path block, challenging block, rest block	9.45 min	Defined brain activation during complex situations
Navigation	Block design: map block, walk block, bifurcation block, rest block	4.20 min	Defined brain activation during navigation and decision making
Visual control	Block design: no obstacle block, obstacle block, bifurcation block	4.30 min	Baseline to control for visual stimuli of the MI paradigms

### 3.7 Data Extraction and Analysis

Means and standard deviations will be calculated for all dependent variables. Histograms and frequency distributions will be constructed to evaluate for normalcy and homogeneity of the distribution of the dependent variables.

#### 3.7.1 Hypothesis 1 (Neural mechanism):

##### 3.7.1.1 fMRI analysis: Preprocessing of imaginary data

Functional data will be pre-processed and analysed with SPM8 (Statistical Parametric Mapping). The first four volumes of each patient's data set will be discarded to allow for T1 equilibration. The remaining functional volumes will be spatially realigned using a least squares approach and a 6 parameter (rigid body) spatial transformation (Friston et al., 1995). Subsequently, the time-series for each voxel will be temporally realigned to the acquisition of the first slice. Images will be normalized to a standard EPI template centered in MNI (Montreal Neurological Institute) space and resampled at an isotropic voxel size of 2 mm. The normalized images will be smoothed with an isotropic 10 mm full-width-at-half-maximum Gaussian kernel.

Anatomical images will be spatially coregistered to the mean of the functional images, spatially normalized by using the same transformation matrix applied to the functional images and finally segmented into grey matter, white matter, CSF and other non-brain partitions (Ashburner & Friston, 2005).

#### 3.7.1.2 First level analysis

The resulting pre-processed fMRI time series will be analysed on a subject-by-subject basis using a block design approach. Statistical maps will be created for each subject using a general linear model (GLM) in which the various activation blocks will be defined as predictors. The model will aim to find regions in which the cerebral response changed as a function of CONDITION. In the obstacle walking paradigm conditions will consist of clear path and obstacle path. In the navigation paradigm conditions will include planning phase, straight walking phase, and bifurcation phase. The visual control paradigm will include watching a path with obstacles, without obstacles, and with bifurcations.

#### 3.7.1.3 Second level analysis

In this level multi-subject analysis will be computed (fixed and corrected random effect). Whole brain analysis will be performed across conditions for each paradigm at two levels: (a) between tasks within group and (b) between two groups.

To explore neural activation differences between conditions and groups, an analysis of covariance (ANCOVA) will be employed. It will be designed per voxel looking for differences between CONDITIONS in each paradigm and between three paradigms within groups and interactions between GROUP and CONDITION, with a family wise-error (FWE) of  $p < .01$  at voxel-level, corrected for multiple comparisons. In order to contrast the three paradigms, the acquisition times will be reconciled. From the "obstacle paradigm" three intervals of a path without obstacles and three

intervals of a path with obstacles will be extracted and shorten to a 30 seconds intervals. From the "navigation paradigm" three intervals of 30 seconds, each including 2 bifurcations will be extracted. From the visual observation paradigm, three intervals of 30 seconds from each condition (path with obstacle, path without obstacle, and path with bifurcation) will be included. Making the duration of all intervals equal (30 seconds) and including three repetitions from each condition will allow us to compare between the paradigms.

Region of interest (ROI) analysis will be considered according to the results obtained from the whole brain analysis and will include areas from frontal, parietal and occipital lobes.

#### 3.7.1.4 fNIRS analysis:

Concentrations of HbO<sub>2</sub> will be analyzed using repeated measures ANOVA's within five tasks (4 walking tasks + 1 standing task) between two groups (health, PD) ( 5 x 2) with alpha set at 0.05. In case of significant interaction effects we will proceed with post hoc Bonferroni tests with alpha set at 0.05. In addition, covariate variables will be assessed by conducting ANCOVA. The covariate variables will be age, gender, and disease severity measured by the UPDRS. Comparison between the two groups while assessing covariate variables may further explore components that affect the ability to walk in complex situations. In order to further explore the effects of cognitive and motor abilities on frontal brain activation an additional analysis that controls for motor and cognitive scores will be conducted. It may be that these indicators are more relevant

that the pathophysiology. Statistical analysis will be performed using SPSS for Windows version 18.

#### 3.7.2 Hypothesis 2 (correlation between cognitive performance and neural activation)

Correlation analysis, Pearson  $r$  or Spearman's rank, will be performed between cognitive performance variables and neural activation variables. The values for each cognitive test e.g., executive function score and TMT, will be correlated with Beta weight values obtained from different contrasts of fMRI paradigms, and levels of HbO<sub>2</sub> in different walking conditions.

#### 3.7.3 Hypothesis 3 (correlation between motor performance and neural activation)

Correlation analysis, Pearson  $r$  or Spearman's rank, will be performed between trail and landing leg distance from obstacle and Beta-weights obtained from the fMRI paradigms and HbO<sub>2</sub> values obtained from the fNIRS protocol. In addition dual task cost variables will be correlated with Beta weight and HbO<sub>2</sub> values.

#### 3.7.4 Hypothesis 4 (The ability of motor-cognitive tests to predict walking performance in complex situations)

Multiple linear regression stepwise analysis will be conducted to evaluate the ability of functional-mobility tests to predict the performance of obstacles negotiation and walking while dual tasking.

## 4 RESULTS

### 4.1 Subject Characteristics

A total of 67 subjects participated in the study (mean age  $71.04 \pm 0.80$ , 37.3 % females). Twenty participants were healthy older adults and 47 participants were persons with PD. Table 5 summarizes the subject characteristics and cognitive and mobility abilities as reflected from the tests performed in the assessment.

No differences were observed between the groups in age and education (Table 5). Persons with PD had lower scores on cognitive tests than the healthy older adults, reflecting specific deficits in executive function. These findings were also apparent in the computerized cognitive tests. In these tests, the scores of the healthy older adults were at expected values with respect to age and education norms (around a score of 100). Persons with PD scored lower in all domains with a prominent deficit in executive function (Table 5).

Similarly, mobility measures were lower in the persons with PD, reflecting deficits in balance and functional mobility (Table 1). Also gait speed and stride length were lower in the patients, compared to the healthy older adults. Time to perform the FSST was twice as long for the persons with PD. Scores on the Mini best and walking distance in two minutes were significantly lower in the persons with PD.

Table 5 *Subjects characteristics*

Domain	Parameters	Healthy older adults (n=20)	PD (n=47)	t (df)	p-value
Characteristics (mean±SE)	Age (yrs)	69.7±1.3	71.7±1.1	-1.1 (65)	0.273
	Education (yrs)	14.5±0.5	14.6±0.5	-0.08 (65)	0.929
	Gender (M/F)	(10/10)	(32/15)		-
Disease severity (mean±SE)	Disease duration (yrs)	-	9.5±1.0		-
	UPDRS motor	-	30.4±2.3		-
	UPDRS total	-	66.2±4.3		-
Cognitive tests Pen & paper (mean±SE)	MMSE	29.3±0.2	28.1±0.3	2.68 (65)	<b>0.008</b>
	TMT A(sec)	59.4±5.1	103.9±10.3	-3.64 (64)	<b>0.001</b>
	TMT B(sec)	111.2±6.4	196.9±15.3	-3.94 (60)	<b>&lt;0.001</b>
	TMT B-A (sec)	51.9±3.9	93±11.5	3.22 (50.7)	<b>0.012</b>
Computerized Cognitive tests (mean±SE)	GCS	101.3±2.1	88.7±1.6	4.56 (64)	<b>&lt;0.001</b>
	Memory	97.6±3.4	87.6±2.4	2.34 (56)	<b>0.023</b>
	Executive Function	102.8±1.8	85.3±1.5	6.53 (64)	<b>&lt;0.001</b>
	Visual Spatial	103.1±3.3	92.7±2.3	2.58 (62)	<b>0.012</b>
	Attention	101.1±1.6	86.1±2.4	3.89 (65)	<b>&lt;0.001</b>
Mobility tests (mean±SE)	Information process	103.6±3.1	92.1±2.8	2.59 (55)	<b>0.012</b>
	FSST (sec)	8.7±0.54	14.7±1.1	-5.40 (60)	<b>&lt;0.001</b>
	MiniBEST	30.7±0.3	22.4±0.9	10.58 (55.5)	<b>&lt;0.001</b>
	2MWT (m)	152.6±4.3	119.0±5.9	5.18 (60.6)	<b>&lt;0.001</b>
Gait characteristics (mean±SE)	Gait speed (cm/sec)	106.9±2.5	95.3±3.6	2.64 (62.7)	<b>0.01</b>
	Stride length (cm)	122.4±2.1	107.9±3.7	3.40 (62.2)	<b>0.014</b>

PD=Parkinson Disease, SE=Standard Error, UPDRS=Unified Parkinson Disease Rating Scale, MMSE=Mini-Mental State Examination, TMT=Trail Making Test, GCS=Global Cognitive Scale, FSST=Four Step Square Test, 2MWT=2 Minute Walk Test.

## 4.2 Motor imagery validation

In order to assess the ability of the participants to imagine, several tests were performed outside of the magnet. Both groups demonstrated sufficient ability of motor imagery as assessed using the KVIQ and chronometric tests (Table 6). Persons with PD reported more difficulty imagining themselves walking as well as lower levels of engagement during the imagery task.

Table 6 *Motor imagery ability\**

Domain	Parameter	Healthy older adults	PD	t-value (df)	p-value
KVIQ (mean±SE)	Visual	23.3±0.5	21.8±0.6	1.59 (54)	0.118
	Kinesthetic	21.3±0.8	20.7±0.7	0.56 (54)	0.577
	Total	44.6±1.1	42.5±1.8	1.09 (54)	0.280
Chronometric* (mean±SE)	Normal vs fast walk	1.13±0.1	1.08±0.05	0.06 (50)	0.513
Debrief (mean±SE)	Easy to imagine <sup>a</sup>	0.95±0.21	2.54±0.36	-3.8 (55.6)	<b>&lt;0.001</b>
	Level of engagement <sup>b</sup>	8.3±0.3	7±0.3	2.47 (57)	<b>0.016</b>
	Only watching video <sup>b</sup>	9.0±0.6	8.7±0.3	0.65 (38)	0.522

\*Further explanations in the methods section p 79

<sup>a</sup> 0=very easy to imagine walking, 10= impossible to imagine walking

<sup>b</sup> 0=no engagement in the virtual scene, 10=very high engagement in the scene

Participants with low motor imagery ability were excluded from the analysis. Low motor imagery ability was defined when one of the criterions below was not met:

1. KVIQ score > 30



2. Debrief question 2 “how difficult was to imagine yourself walking” < 6
3. Debrief question 4 “what percent of time you imagine yourself walking” > 50%
4. Chronometric test > 0

Based on these scores, one healthy older adult and four persons with PD were defined as having low motor imagery ability and were excluded from the fMRI analyses.

#### 4.3 Objective 1:

To assess the neural mechanisms underlying walking in complex situations such as negotiating obstacles and dual task, subjects were asked to imagine themselves walking in three different virtual scenes of a park landscape. The virtual scenes differ in the paths of the park landscape: 1) clear path reflects usual walking; 2) the path with obstacles; and 3) paths with intersections presenting walking while navigating to a specific target shown on a map. In order to control for neural activation related to visual aspects of the virtual scene, participants were also provided with a second task in which they were asked to only watch the movie without imagining walking in it. The order of the scenes were standardized and fixed for all participants. Thus, the analysis included (1) contrasts between imagery walking and watching each virtual scene within each group and between the groups and (2) contrasts between the imagery walking scenes within each group. The fMRI tests were performed by a subgroup of 20 persons with PD and 20 healthy older adults.

To investigate the role of the frontal lobe in real walking in complex situations, the fNIRS system was used. Two probes were located on the subjects' forehead while performing five tasks; four walking tasks and one control task. The walking tasks included usual walking, walking while serially subtracting 3s, walking while negotiating obstacles, and walking while counting. The control task was standing while serially subtracting 3s. Thus, the analyses included comparisons between the tasks within each group and between the groups.

The results include six parts; the first five parts include the fMRI and the sixth part the fNIRS:

1. The neural mechanisms underlying usual walking, comparison between imagined walking and watching.
2. The neural mechanisms underlying walking while negotiating obstacles, comparison between imagined walking and watching.
3. The neural mechanisms underlying walking while navigating to a target, comparison between imagined walking and watching.
4. Differences between imagined walking tasks, comparison between imagined usual walking and walking while negotiating obstacles.
5. Differences between imagined walking tasks, comparison between imagined usual walking and walking while navigating to a target.
6. The role of the frontal lobe in complex walking tasks as measured using fNIRS.

### 4.3.1 The brain regions activated during usual walking, comparison between imagined walking and watching

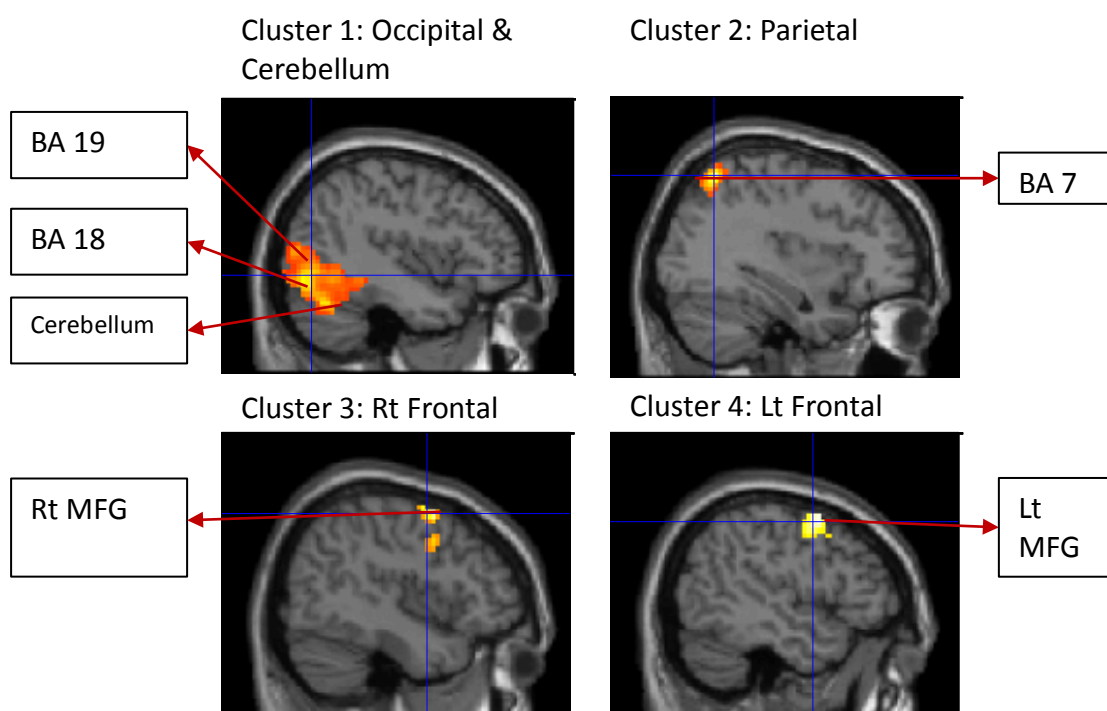
#### 4.3.1.1 Healthy older adults

A comparison between imagined usual walking and watching the same scene revealed higher brain activation in the frontal, parietal, occipital, lobes and cerebellum during imagined walking (Table 7). Four clusters passed the family-wise error test (FWE). Table 7 summarizes the distribution of voxel sizes in the different clusters and their contribution to the activation during the task. As seen, the largest cluster includes the occipital, and cerebellum lobes (cluster 1). Although occipital activation also took place during usual watching of the scene, higher activation related to visual-spatial aspects of walking was seen in this cluster. The second cluster includes the parietal lobe and it is probably associated with integrating and processing the incoming information. The third and fourth clusters include the frontal lobe and their activation relates to cognitive aspects of walking.

*Table 7 The clusters that were more activated during imagined usual walking compare to watching in healthy older adults*

Cluster	FWE-p	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.000	2850	Occipital	1687	BA 18	189	
					BA 19	252	(-21,-94,-17)
					IOG	224	(-36, -88, -5)
			Cerebellum	>531	Post lobe	531	(-39,-64,-26)
					Ant lobe	200	( 0, -60, -30)
2	0.000	710	Parietal	383	BA 7	213	( 36,-61, 58)
					Precuneus	113	( -6, -67, 61)
3	0.005	143	Frontal	133	BA 6	33	( 48, 5, 55)
					BA 9	15	( 45, 5, 40)
					MFG	101	( 39, -1, 64)
4	0.003	157	Frontal	153	MFG	105	( -48, 5, 52)
					BA 6	50	( -39, -1, 46)

The figures below represent the four clusters that were more activated during imagine usual walking in healthy older adults. Cluster 1 demonstrates increased activation in middle occipital gyrus (MOG) and inferior occipital gyrus (IOG) corresponding to BA 18 and BA 19, and cerebellum post lobe on both left and right hemispheres. Cluster 2 shows increased activation in superior parietal lobe (SPL) corresponding to precuneues and BA7. Cluster 3 and 4 demonstrate increased activation in middle frontal gyrus (MFG) corresponding to BA 6 and BA 9.



**Figure 11:** The clusters activated during imagined usual walking vs. watching in healthy older adults

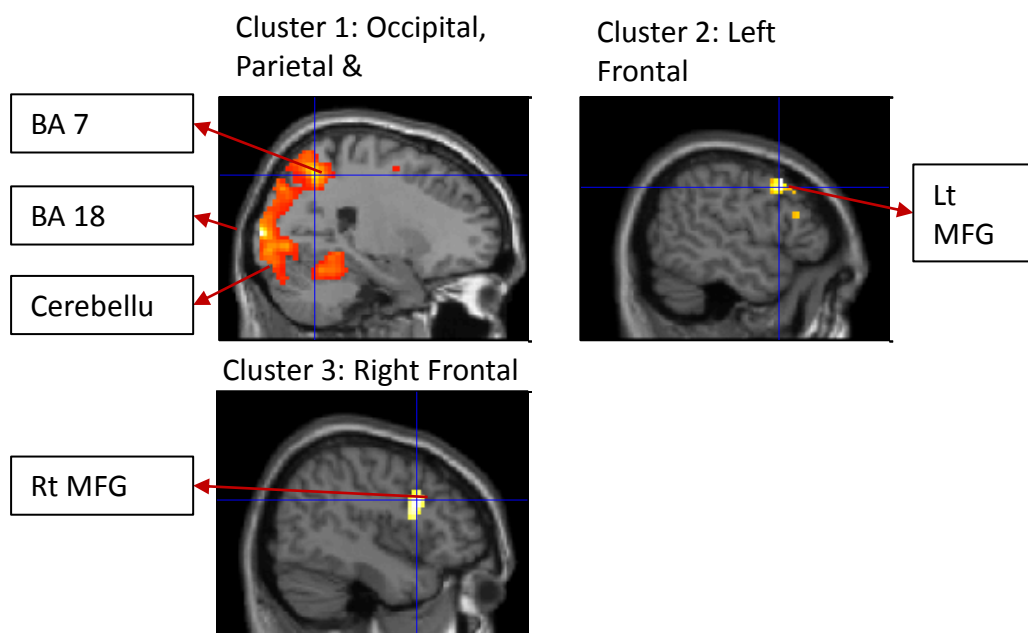
#### 4.3.1.2 Persons with PD

A comparison between imagined usual walking and watching the same scene demonstrated higher brain activation in the occipital, parietal, frontal lobes, and cerebellum during imagined usual walking. This increased activation was seen in three clusters that passed family-wise error tests (FWE). Table 8 summarizes the distribution of voxel sizes in the different clusters and their contribution to the activation during the task. One large cluster (cluster 1) includes secondary visual areas in the occipital lobe, integrating structures in the parietal lobe, and areas related to locomotion in the cerebellum. Clusters 2 and 3 contain the frontal lobe that plays an important role in the cognitive aspects of imagined walking.

*Table 8 The clusters activated during imagined usual walking compare to watching in persons with PD*

Cluster	FWE p	Total voxel	Main Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.000	6601	Occipital	2367	BA 18	249	(-21, -97, 7)
							( 24, -97, 7)
					BA 19	428	( 36,-82,-11)
			Parietal	1799			(-36,-82,-11)
					SOG	65	( 36, -79, 25)
					Precuneus	696	( 24, -59, 55)
							( -24,-52, 45)
					BA 7	470	( 24, -60, 43)
							(-24, -56, 46)
			Cerebellum	>782	IPL	422	(-37, -66, 46)
Post lobe	782	(-15,-78, -23)					
		( 29,-74, -29)					
	Ant lobe	274			( 29,-44, -23)		
					(-29,-53, -23)		
		Limbic	34	Para-hippocampa	32	( 24,-48, -12)	
2	0.002	145	Left Frontal	144	MFG	75	(-51, 14, 43)
					BA 9	29	(-39, 41, 37)
					IFG	46	(-39, 5, 28)
3	0.049	71	Right Frontal	71	IFG	15	( 45, 14, 28)
					MFG	18	( 44, 3, 46)

The figures below illustrate the three clusters that were more activated during imagined usual walking in the persons with PD, compared to observation. Cluster 1 presents increase activation in middle and inferior occipital gyrus (MOG & IOG) corresponding to BA 18 and BA 19 in both right and left hemispheres, inferior and superior parietal lobules (IPL & SPL) corresponding to precuneus and BA 7 in both right and left hemispheres, and cerebellum posterior and anterior lobes in both right and left lobes. Cluster 2 demonstrates increase activation in left middle and inferior frontal gyrus (MFG & IFG) corresponding to BA 9 whereas cluster 3 represents the right MFG and IFG.



**Figure 12:** The clusters activated during imagined usual walking vs. watching in persons with PD

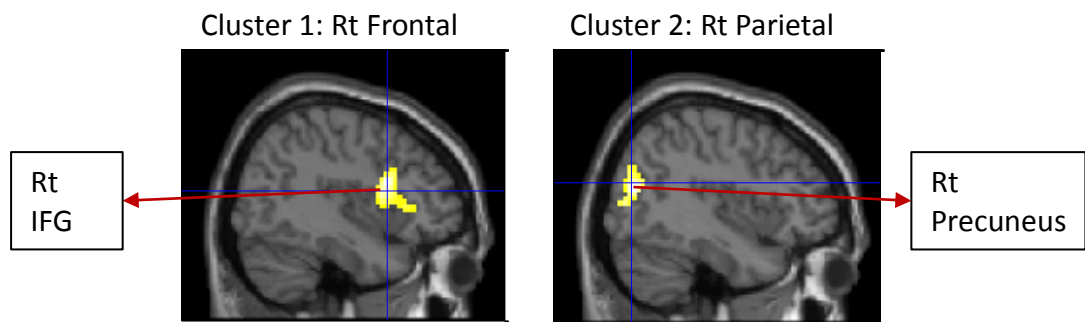
#### 4.3.1.3 Persons with PD compared to healthy older adults

A comparison between persons with PD and healthy older adults in imagined usual walking vs only watching revealed higher brain activation in persons with PD in right frontal, parietal, temporal, and occipital lobes during imagined usual walking. This increased activation was shown in two clusters that passed family-wise error test (FWE). There were no brain areas that were more activated in healthy older adults. Table 9 summarizes the distribution of voxel sizes in the different clusters and their contribution to the activation during the task.

*Table 9 The clusters that were more activated during imagined usual walking in persons with PD compare to healthy older adults*

Cluster	FWEp value	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.020	162	Right Frontal	136	IFG	37	( 45, 26, 1)
					Insula	26	( 42, 7, 13)
					Precentral	25	( 45, 16, 8)
2	0.039	141	Right Parietal Temporal Occipital	40	Precuneus	36	(30,-79,37)
					MTG	58	(42,-73,16)
					BA 19	24	( 41,-79, 6)

The figures below illustrate the two clusters that were more activated in persons with PD during imagined usual walking. Cluster 1 shows increase activation in right inferior frontal gyrus (IFG), insula, and precentral gyrus. Cluster 2 presents increase activation in the right parietal lobe corresponding to precuneus, right middle temporal gyrus (MTG), and right MOG corresponding to BA 19.



**Figure 13:** The clusters activated during imagined usual walking compare to watching in persons with PD vs Healthy older adults

#### 4.3.1.4 Summary:

The brain regions activated during imagined usual walking in both healthy older adults and persons with PD include the middle occipital gyrus (mainly BA 18 & 19), the superior parietal lobe (mainly the precuneus), the middle frontal gyrus (mainly BA 6 & 9), and the cerebellum post lobe. The comparison between groups revealed higher activation in persons with PD in right inferior frontal gyrus, precuneus, middle temporal gyrus, and BA 19.

#### 4.3.2 The brain regions activated during imagined walking while negotiating obstacles, comparison between imagined walking and watching

##### 4.3.2.1 Healthy older adults

A comparison between imagined walking while negotiating obstacles and watching the same scene revealed higher brain activation in frontal, parietal, occipital and cerebellum areas during imagined walking while negotiating obstacles. Three clusters passed family-wise error tests (FWE). Table 10 demonstrates the distribution of voxel sizes in the different clusters and their contribution to the activation during the task. As



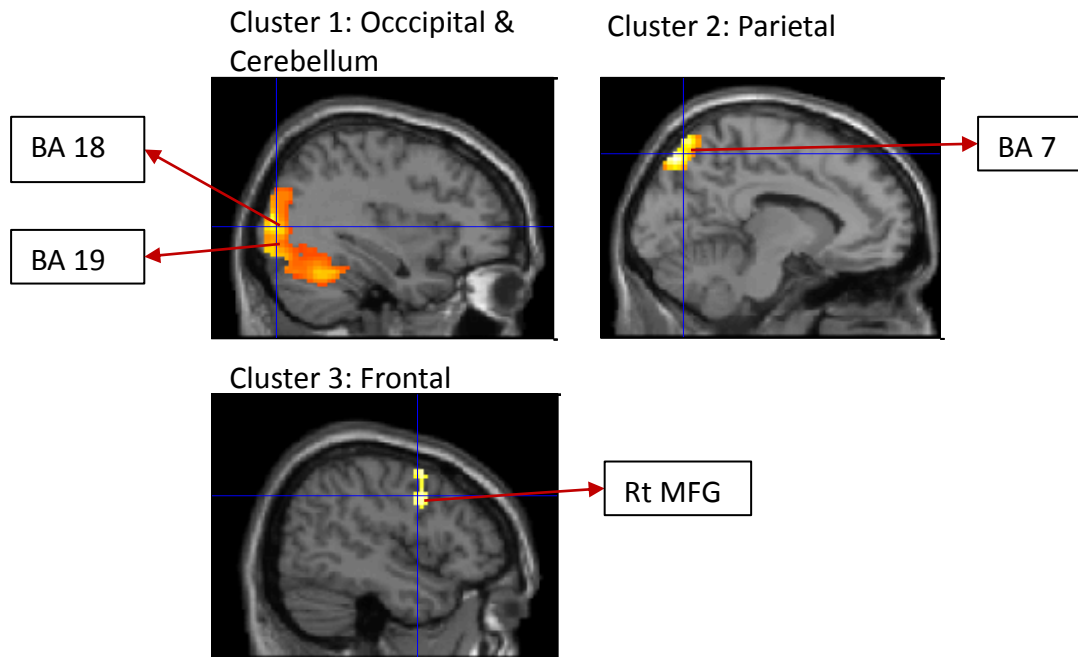
seen the largest cluster contains the occipital lobe and cerebellum (cluster 1) the second cluster includes the parietal lobe and the third cluster the frontal lobe.

*Table 10 The clusters that were more activated during imagery walking while negotiating obstacles compared to watching in healthy older adults*

Cluster	FWEp value	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.000	3989	Occipital	1969	BA 19	321	( 39, -81, -9)
					IOG	236	(-39,-75,-12)
					BA 18	202	( 36, -88,10)
			Cerebellum	>973	MOG	690	( -30, -90, 1)
					Post Lobe	973	( 39,-60,-24)
							(-39,-64,-23)
					Ant Lobe	383	(-28,-59,-30)
2	0.000	810	Parietal	478			( 33,-55,-30)
							( 24,-43,-14)
					Para-hippocampa	21	
					BA 7	251	( 36,-61,58)
3	0.016	164	Frontal	155	SPL	209	(-20,-69,58)
					Precuneus	251	( 17,-64,56)
					MFG	108	( 36, -1, 64)
					BA 6	32	( 51, 5, 52)
							( -45, 3, 52)
					BA 9	23	( 48, 5, 37)
					IFG	41	

The figures below represent the three clusters that were more activated during imagery walking while negotiating obstacles in healthy older adults. Cluster 1 demonstrates increased activation in MOG and IOG, corresponding to BA 18 and BA 19, and cerebellum posterior and anterior lobes on both left and right hemispheres. In addition, increased activation was demonstrated in the limbic lobe corresponding to parahippocampa gyrus. Cluster 2 represents increased activation in superior parietal lobe (SPL) corresponding to precuneues and BA7. Cluster 3 demonstrates increased activation in middle frontal gyrus (MFG)

corresponding to BA 6 and inferior frontal gyrus (IFG) corresponding to BA 9.



**Figure 14:** The clusters activated during imagined walking while negotiating obstacles vs. watching in healthy older adults

#### 4.3.2.2 Persons with PD

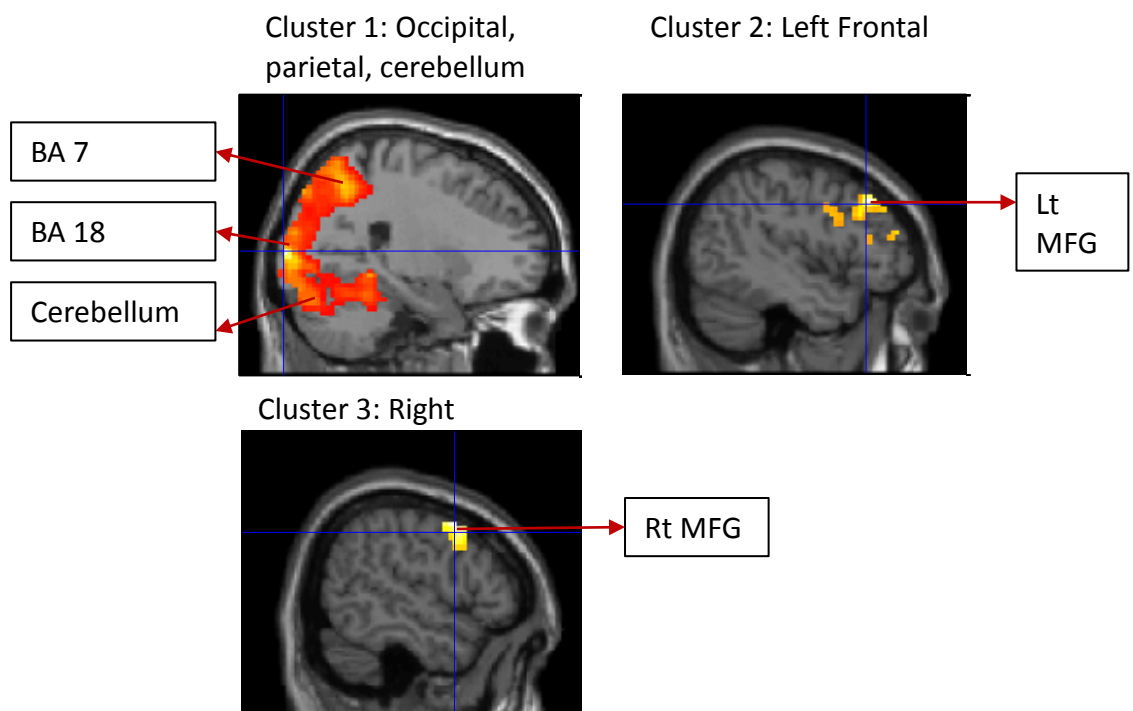
A comparison between imagined walking while negotiating obstacles and watching the same scene demonstrated higher brain activation in the occipital, parietal, frontal, limbic, and cerebellum lobes during imagined walking while negotiating obstacles. Cluster 1 includes the occipital, parietal, limbic, and cerebellum lobes, cluster 2 includes the left frontal lobe, and cluster 3 the right frontal lobe. Table 11 summarizes the distribution of voxel sizes in the different clusters and their contribution to the activation during the task.

*Table 11: The clusters that were more activated during imagined walking while negotiating obstacles compare to watching in subject with PD*

Cluster	FWE p value	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.000	7922	Occipital	2669	BA 18	286	( 24,-97, 7)
					MOG	802	(-24,-94, 4)
							( 32,-92, 4)
					BA 19	459	( 32,-87, 3)
			Parietal	2021			(-43,-77, 3)
					Precuneus	827	(31,-75, 37)
							(-24,-82,37)
					BA 7	560	(27,-56, 47)
					SPL	472	(-24,-56,47)
					IPL	372	(-36,-51,47)
			Cerebellum	>1020	BA 40	166	
					Post lobe	1020	( 43,-65,-24)
							(-39,-68,-24)
					Ant lobe	387	( 27,-47,-24)
			Limbic	44			(-33,-59,-24)
					Para-hippocampa	40	(-33,-48,-10)
2	0.025	276	Left Frontal	275	MFG	159	(-45, 29, 40)
					IFG	52	(-54, 14, 40)
					BA9	43	(-38, 37, 35)
					BA 10	12	(-38, 52, 17)
3	0.010	337	Right Frontal	335	MFG	171	( 27, -4, 55)
					IFG	82	( 45, 14, 25)
					BA 6	50	( 54, 8, 49)
					BA 9	36	( 51, 8, 38)

The figures below represent the three clusters that were more activated during imagined walking while negotiating obstacles. Cluster 1 demonstrates increase activation in middle occipital gyrus (MOG) corresponding to BA 18 and BA 19 in both right and left hemispheres, inferior and superior parietal lobules (IPL & SPL) corresponding to precuneus, BA 7 and BA 40 in both right and left hemispheres, para-hippocampa gyrus, and cerebellum posterior and anterior lobes in both

right and left lobes. Cluster 2 presents increase activation in left middle and inferior frontal gyrus (MFG & IFG) corresponding to left BA 9, BA 10. Clusters 3 shows increase activation in right middle and inferior frontal gyrus corresponding to BA 6 and BA 9.



**Figure 15:** The clusters activated during imagined walking while negotiating obstacles vs. watching in persons with PD

#### 4.3.2.3 Persons with PD compared to healthy older adults

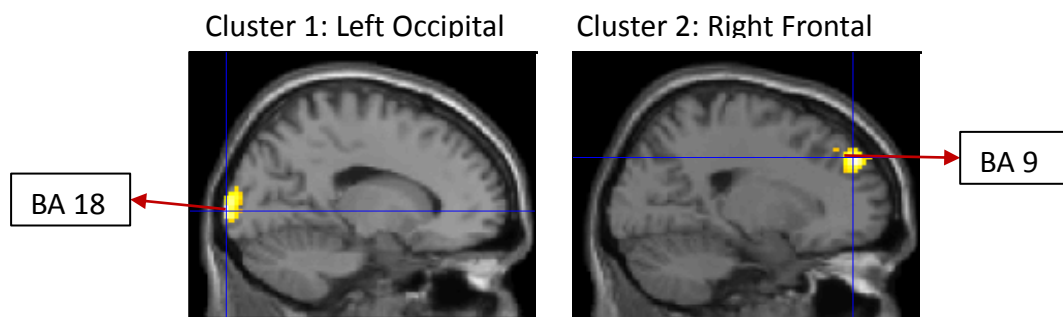
A comparison between persons with PD and healthy older adults in imagined walking while negotiating obstacles vs only watching demonstrated higher brain activation in persons with PD in the occipital and frontal lobes during imagined walking while negotiating obstacles. This activation is presented in two clusters, one that passed FWE correction and one that demonstrated trend tower significant ( $p=0.086$ ). Table 12 summarizes the distribution of voxel sizes in the different clusters and their

contribution to the activation during the task. As seen the first cluster includes the left occipital lobe and clusters 2 the right frontal lobe.

*Table 12: The clusters that were more activated in persons with PD compared to healthy older adults during imagined walking while negotiating obstacles*

Cluster	FWE p	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.036	225	Left Occipital	196	BA 18 MOG	65 57	( 14,-103,1) (-15,-103,1)
2	0.086	189	Right Frontal	168	SFG BA 8 BA 9	143 34 27	( 21, 50, 37) ( 24, 41, 43) ( 27, 44, 40)

The figures below represent the two clusters that were more activated during imagined walking while negotiating obstacles. Cluster 1 demonstrates increase activation in left MOG and BA 18 both associated with visual-spatial components of walking. Cluster 2 represents increase activation in right superior frontal gyrus (SFG) corresponding to BA 8 & 9.



**Figure 16:** The clusters activated during imagined walking while negotiating obstacles in patient with PD vs. healthy older adults

#### 4.3.2.4 Summary:

The brain regions activated during imagined walking while negotiating obstacles in both healthy older adults and persons with PD includes the middle occipital gyrus, mainly BA 18, superior parietal lobe, mainly the precuneus, and BA 7, cerebellum post lobe, limbic lobe mainly the para-hippocampa gyrus, and superior frontal gyrus. However, comparison between groups demonstrated higher activation in persons with PD in BA 18, BA 8 and BA 9.

### 4.3.3 The brain regions activated during imagined walking while navigating, comparison between imagined walking and watching

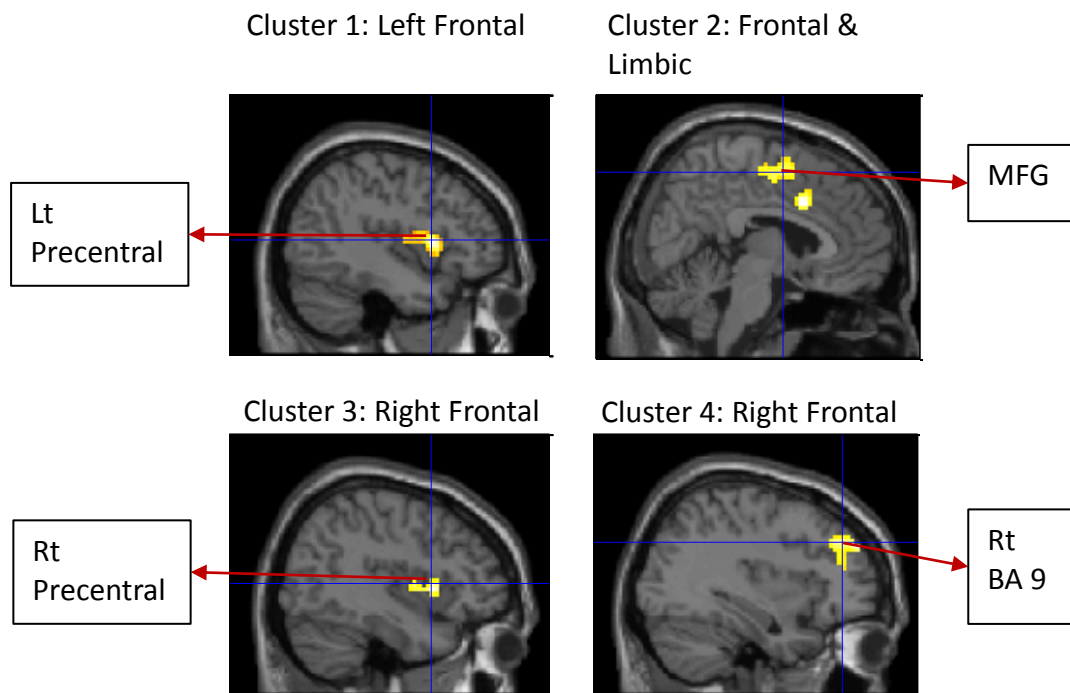
#### 4.3.3.1 Healthy older adults

A comparison between imagined walking while navigating to specific target and watching the same scene revealed higher brain activation in the frontal and limbic lobes during imagine walking while navigating. Three clusters passed family-wise error test (FWE) and one cluster demonstrated trend toward significant. Table 13 summarizes the distribution of voxel sizes in the different clusters and their contribution to the activation during the task. As seen, the frontal lobe is included in all four clusters.

*Table 13: The four clusters that were activated during imagery walking while navigating compare to watching in healthy older adults*

Cluster	FWEp value	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.000	257	Left Frontal	105	Precentral	81	(-42,11, 7)
					IFG	16	(-48,14,-1)
					Left Insula	76	(-32,19,-1)
2	0.000	257	Frontal	165	BA 6	54	( 3, -7, 52)
					MFG	105	( 2, -7, 55)
					SMA	142	(-4, -6, 55)
					Cingulate gyrus	121	( 6, 11,34)
3	0.003	135	Right Frontal	49	Precentral	28	(-6, 14,37)
					IFG	20	(60, 8, 16)
					Rt Insula	59	(42, 11, 1)
4	0.076	135	Right Frontal	58	MFG	33	(33, 35,34)
					BA 9	24	(36, 50,31)
					SFG	25	

The figures below represent the four clusters that were more activated during imagined walking while navigating in healthy older adults. Cluster 1 demonstrates increase activation in left inferior frontal gyrus (IFG) corresponding to precentral gyrus, and left insula corresponding to BA 13. Cluster 2 represents increase activation in middle frontal gyrus (MFG) corresponding to BA 6, SMA and cingulate gyrus on both right and left hemispheres. Cluster 3 shows increase activation in right inferior frontal gyrus (IFG) corresponding to precentral gyrus, and right insula corresponding to BA 13. Cluster 4 demonstrates increase activation in MFG and SFG corresponding to BA 9 on the right hemisphere.



**Figure 17:** The clusters activated during imagined walking while navigating vs. watching in healthy older adults

#### 4.3.3.2 Persons with PD

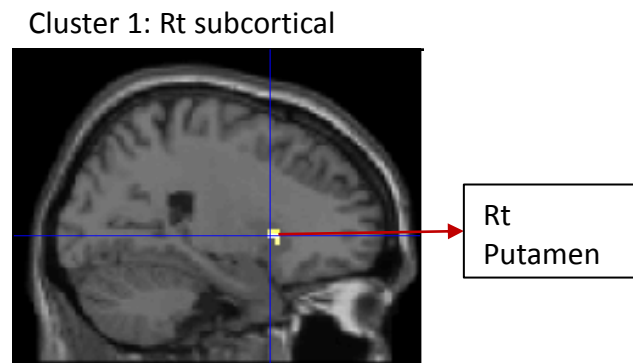
A comparison between imagined walking while navigating and watching the same scene in persons with PD did not demonstrate clusters that passed FWE test. However, applying FDR of p value 0.05 revealed higher activation in one cluster that includes the right putamen during imagine walking while navigating. Table 14 summarizes the distribution of voxel sizes in the cluster and their contribution to the activation during the task.



*Table 14: Comparison between imagined walking while navigating and watching in persons with PD*

Cluster	FDR	Total voxel	Lobe	Brain areas	Size	MNI (x,y,z)
1	0.05	14	Rt Sub-cortical	Putamen	9	(23,12,1)

The figure below represents the cluster of right putamen that was more activated during imagined walking while navigating in persons with PD.



**Figure 18:** The cluster activated during imagined walking while navigating vs. watching in persons with PD

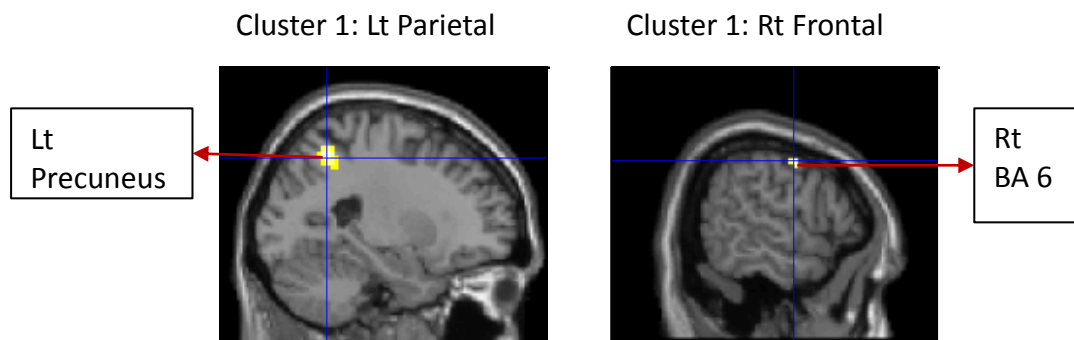
#### 4.3.3.3 Persons with PD compared to healthy older adults

A comparison between persons with PD and healthy older adults in imagined walking while navigating vs only watching demonstrated increased activation in parietal and frontal lobes in healthy older adults. Two clusters passed FDR test, one includes the left parietal lobe and one the right frontal lobe. Table 15 demonstrates the distribution of voxel sizes in the different clusters and their contribution to the activation during the task.

*Table 15: The clusters that were more activated during imagined walking while navigating in healthy older adults compared to PD patients*

Cluster	FDR	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.047	54	Left Parietal	54	Precuneus BA 7	32 13	(-24,-55,49)
2	0.047	8	Right Frontal	7	BA 6 Precentral	7 6	( 60, -4,46)

The figures below represent the two clusters that were more activated during imagine walking while navigating in healthy older adults compare to persons with PD. Cluster 1 demonstrates increased activation in left precuneus and cluster 2 in right BA 6 and precentral gyrus.



**Figure 19:** The clusters activated during imagined walking while navigating in healthy older adults vs. persons with PD

#### 4.3.3.4 Summary:

The brain regions activated during imagined walking while navigating in healthy older adults includes frontal areas such as the supplementary motor area (SMA), precentral gyrus, BA 6 & 9, the insula, and the cingulate gyrus in the limbic lobe. However, in persons with PD increased activation, compared to watching a scene, was observed only in

the putamen. Comparison between groups demonstrated higher activation in healthy older adults in BA 6 and precuneus.

#### 4.3.4 Differences between imagined walking while negotiating obstacles and imagined usual walking

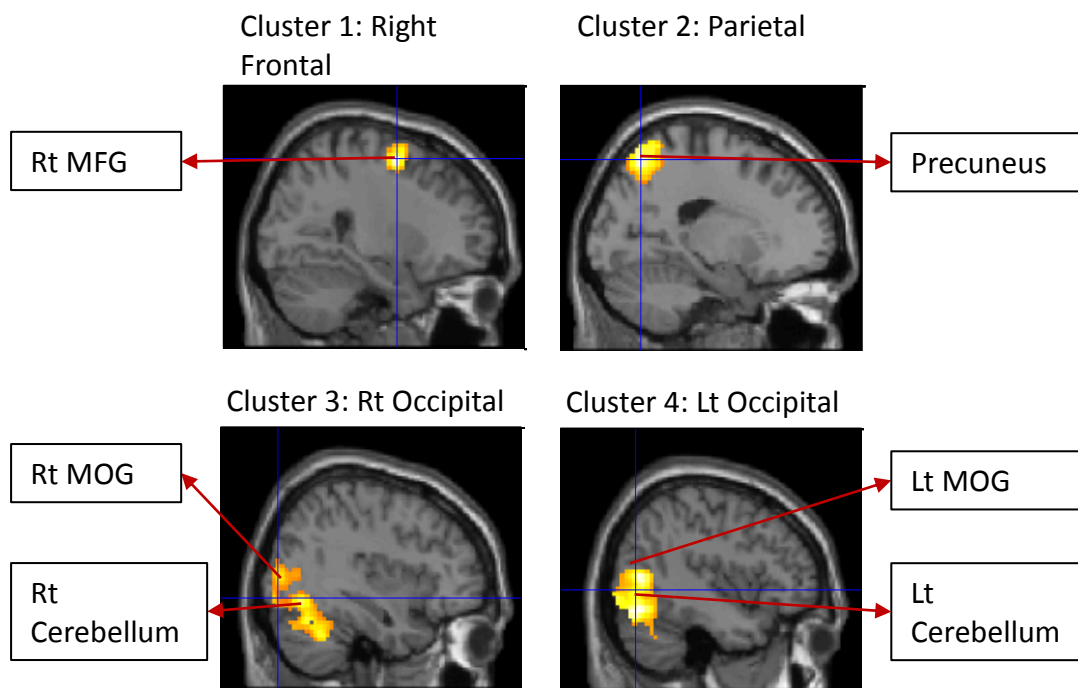
##### 4.3.4.1 Healthy older adults

A comparison between imagined walking while negotiating obstacles and imagined usual walking revealed higher activation in the frontal, parietal, occipital, and cerebellum lobes during imagined walking while negotiating obstacles. Four clusters passed family-wise error test (FWE). Table 16 summarizes the distribution of voxel sizes in the clusters and their contribution to the activation during the task.

*Table 16: The clusters that were more activated during imagined walking while negotiating obstacles compare to usual walking in healthy older adults*

Cluster	FWE p	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.001	314	Right Frontal	288	MFG	158	( 27,-1,58)
					BA 6	131	( 6, -7, 70)
					SFG	53	( 5, -7, 70)
					SMA	72	
2	0.000	784	Parietal	567	Precuneus	298	(18,-61, 52)
					BA 7	248	(12,-60, 63)
					SPL	182	(-18,-67,58)
3	0.000	648	Right Occipital	285	MOG	146	( 42, -80, 3)
					BA 19	51	
					IOG	41	(38,-85,-10)
			Cerebellum	>272	BA 18	21	
					Post	204	(42, -64,-23)
4	0.000	623	Left Occipital	347	Ant	68	(36, -55,-32)
					MOG	139	(-48, -75, -5)
					IOG	92	(-34,-86,-11)
			Cerebellum	>111	BA 18	31	
					BA 19	66	(-41,-80,-11)
					Post	111	(-32,-62,-19)

The figures below represent the four clusters that were more activated during imagine walking while negotiating obstacles compare to imagine usual walking in healthy older adults. Cluster 1 shows increase activation in the right MFG and SFG, corresponding to BA 6 and SMA. Cluster 2 demonstrates increase activation in the parietal lobe, specifically in the precuneus and BA 7. Cluster 3 and 4 represents increase activation in SOG and IOG, corresponding to BA 18 and BA 19, and cerebellum posterior lobule in both right and left hemispheres.



**Figure 20:** The clusters activated during imagined walking while negotiating obstacles vs. usual walking in healthy older adults

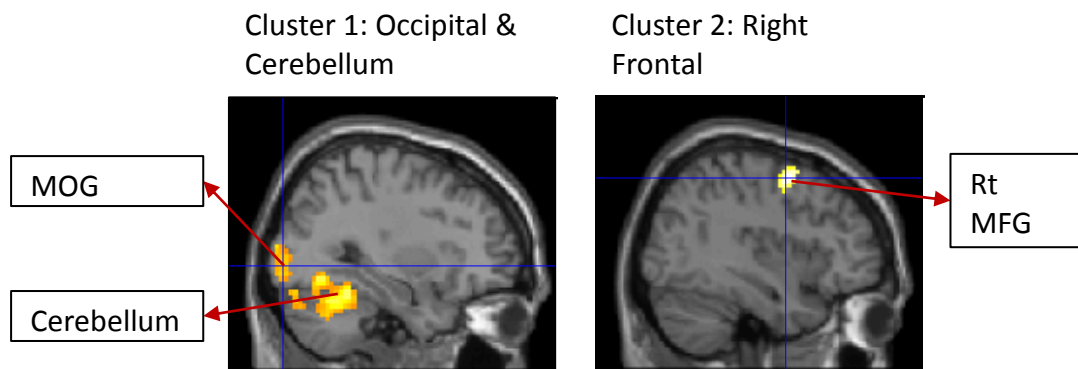
#### 4.3.4.2 Persons with PD

A comparison between imagined walking while negotiating obstacles and imagined usual walking in persons with PD revealed higher activation in the occipital, cerebellum, and frontal lobes during imagined walking while negotiating obstacles. Two clusters passed family-wise error test (FWE). Table 17 summarizes the distribution of voxel sizes in the clusters and their contribution to the activation during the task.

*Table 17: The clusters that were more activated during imagined walking while negotiating obstacles compare to usual walking in persons with PD*

Cluster	FWE p	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.000	1107	Occipital	375	MOG	114	( 34,-91,-1)
					BA 18	67	( -29,-91,-1)
					BA 19	48	( 39,-79,-20)
			Cerebellum	>619			(-32,-81,-20)
					Post	525	(-39,-64,-26)
					Ant	94	( 38,-64,-26)
2	0.005	138	Right Frontal	134	MFG	116	( 39, 2, 55)
					BA 6	51	( 43, 3, 58)

The figures below represent the two clusters that were more activated during imagine walking while negotiating obstacles compare to imagine usual walking in persons with PD. Cluster 1 shows increase activation in MOG, corresponding to BA 18 and BA 19, and cerebellum posterior and anterior lobules in both right and left hemispheres. Cluster 2 presents increase activation in right MFG, corresponding to BA 6.



**Figure 21:** The clusters activated during imagined walking while negotiating obstacles vs. usual walking in persons with PD

#### 4.3.4.3 Summary:

Increased activation in MFG and MOG was found during imagined walking while negotiating obstacles compare to imagine usual walking in both groups. However, healthy older adults demonstrated increased activation also in the precuneus and BA 7 in the parietal lobe, and bilateral SMA in the frontal lobe.

#### 4.3.5 Differences between imagined walking while navigating and imagined usual walking

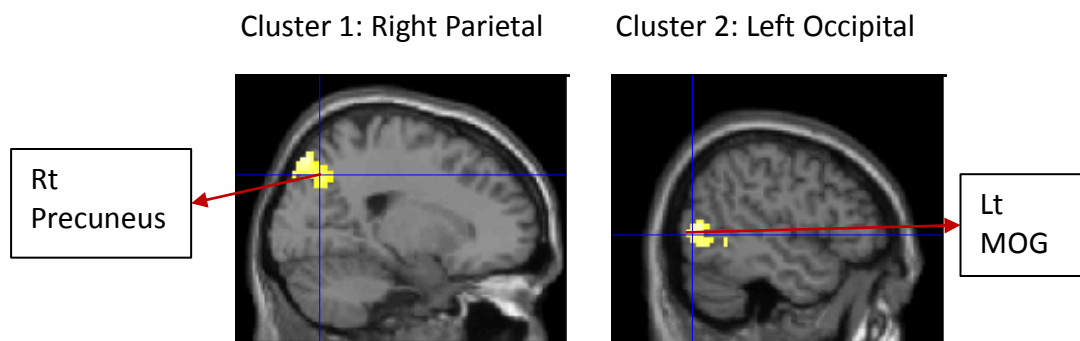
##### 4.3.5.1 Healthy older adults

Comparison between imagined walking while navigating to specific target and imagine usual walking demonstrated higher brain activation in parietal and occipital lobes during imagine walking while navigating. Two clusters passed FWE test. Table 18 summarizes the distribution of voxel sizes in the different clusters and their contribution to the activation during the task.

*Table 18: The clusters that were more activated during imagery walking while navigating compared to usual walking in healthy older adults*

Cluster	FWEp value	Total voxel	Lobe	Lobe size	Brain areas	Size	MNI (x,y,z)
1	0.001	200	Right	93	Precuneus	82	(21,-70,40)
			Parietal		BA 7	45	(21,-77,47)
			Right	43	BA 19	16	(32,-83,24)
			Occipital				
2	0.023	100	Left	40	MOG	31	(-51,-70,1)
			Occipital				

The figures below represent the two clusters that were more activated during imagined walking while navigating compare to imagined usual walking in healthy older adults. Cluster 1 represents increase activation in right precuneus and BA 7, and right BA 19 in the occipital lobe. Cluster 2 shows increase activation in left MOG.



**Figure 21:** The clusters activated during imagined walking while navigating vs. usual walking in healthy older adults

#### 4.3.5.2 Persons with PD

A comparison between imagined walking while navigating and imagined usual walking in persons with PD demonstrated no differences in brain activation. Persons with PD did not increase brain activation during imagined walking while navigating.

#### 4.3.5.3 Summary:

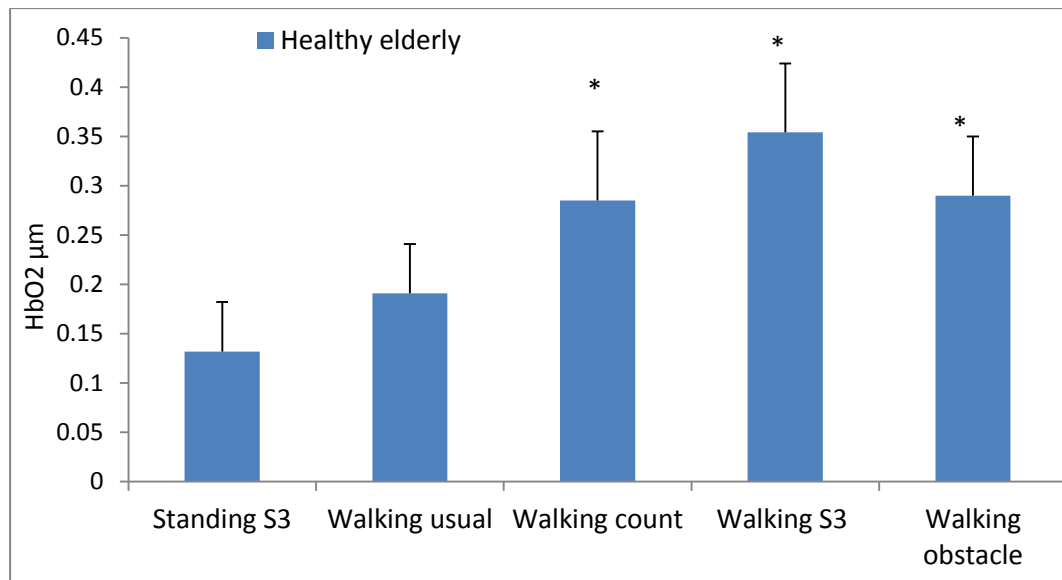
A comparison between imagined walking while navigating and imagined usual walking, demonstrated higher activation in right precuneus and BA 7, and bilateral MOG only in the healthy older adults. No differences in neural activation between imagined walking tasks were presented in persons with PD.

### 4.3.6 The role of the frontal lobe in complex walking tasks as measured using fNIRS

#### 4.3.6.1 Healthy older adults

Significant differences in HbO<sub>2</sub> levels were seen between the five tasks ( $p < 0.001$ ). Comparison between each task to usual walking revealed significant increase in HbO<sub>2</sub> level during walking while counting forward ( $p = 0.035$ ), walking while serially subtracting 3s ( $p = 0.016$ ), and walking while negotiating obstacles ( $p = 0.019$ ). No significant change in HbO<sub>2</sub> level was demonstrated during standing while serially subtracting 3s ( $p = 0.962$ ) (Table 19). Figure 23 illustrates the changes in HbO<sub>2</sub> level during the different tasks.



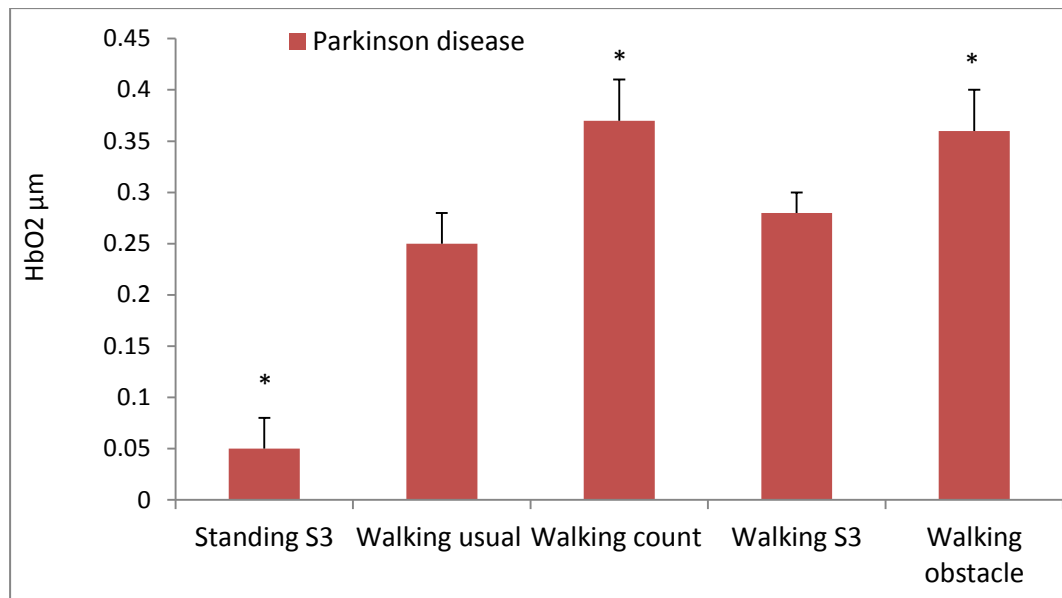


**Figure 22:** HbO<sub>2</sub> levels in healthy older adults

HbO<sub>2</sub> level during the five tasks in the healthy older adults. The \* indicates a significant difference compared to usual walking

#### 4.3.6.2 Persons with PD

Significant differences in HbO<sub>2</sub> levels were seen between the five tasks ( $p < 0.001$ ). Comparison between each task to usual walking revealed significant increase in HbO<sub>2</sub> level during walking while counting forward ( $p = 0.006$ ) and walking while negotiating obstacles ( $p < 0.001$ ). No significant change in HbO<sub>2</sub> level was demonstrated during walking while subtracting 3s ( $p = 0.278$ ) and a significant decrease in HbO<sub>2</sub> was shown during standing while serially subtracting 3s ( $p < 0.001$ ) (Table 19). Figure 24 represents the changes in HbO<sub>2</sub> level during the different tasks.



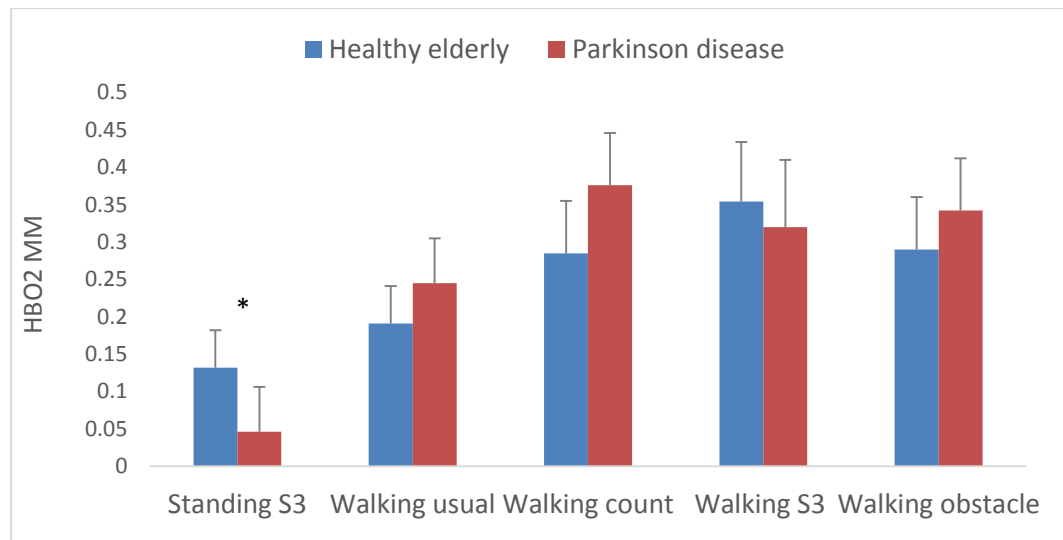
**Figure 23:** HbO<sub>2</sub> levels in persons with PD

HbO<sub>2</sub> level during the five tasks in persons with PD. The \* indicates a significant difference compared to usual walking

#### 4.3.6.3 Persons with PD compared to healthy older adults

Persons with PD demonstrated trend toward significant higher level of HbO<sub>2</sub> during usual walking ( $p=0.084$ ) and significant lower level of HbO<sub>2</sub> during standing while subtracting 3s ( $p=0.019$ ) compare to healthy older adults. No significant differences between the groups were found during walking while counting ( $p=0.293$ ), walking while subtracting 3s ( $p=0.279$ ), and walking while negotiating obstacles ( $p=0.285$ ). As shown in figure 25 both groups presented significant increase in HbO<sub>2</sub> level during walking while negotiating obstacles and counting forward compare to usual walking. However, significant increase in HbO<sub>2</sub> level during walking while subtracting 3s compare to usual walking was shown only in healthy older adults ( $p=0.016$ ) and significant decrease in HbO<sub>2</sub> level during standing

while subtracting 3s was found only in persons with PD ( $p<0.001$ ). Table 19 below summarize the statistics results.



**Figure 24:** HbO<sub>2</sub> levels in both groups

HbO<sub>2</sub> levels during the five tasks in both groups. The \* indicates a significant difference between the groups.

*Table 19: HbO<sub>2</sub> levels during the different tasks in each group and statistics*

Task (HbO <sub>2</sub> μm)	Healthy older adults (HbO <sub>2</sub> μm ± SE)	Persons with PD (HbO <sub>2</sub> μm ± SE)	One way ANOVA between groups (p)	Paired t- test* HC (p)	Paired t-test* PD (p)
Standing S3	0.13±0.05	0.05±0.03	<b>0.019</b>	0.962	<b>&lt;0.001</b>
Usual walk	0.19±0.05	0.25±0.03	0.084	-	-
Counting	0.29±0.07	0.38±0.04	0.293	<b>0.035</b>	<b>0.006</b>
DT walk	0.36±0.07	0.32±0.05	0.279	<b>0.016</b>	0.278
Obstacle walk	0.29±0.06	0.34±0.04	0.285	<b>0.019</b>	<b>&lt;0.001</b>
DT vs. Obstacle				0.209	0.080
DT vs. counting				0.302	<b>0.016</b>

\*Each condition compare to usual walking

#### 4.3.6.4 Correlations between HbO<sub>2</sub> level, dual task performance and dual task cost

Dual task performance was defined as (percent successful subtractions/duration) and it is presented in Table 20. Dual task performance was better in the healthy older adults compare to the persons with PD ( $p=0.019$ ). During walking while subtracting 3s the dual task cost on gait speed and stride length was significantly higher in persons with PD compared to healthy older adults ( $p<0.001$ ). No differences in dual task cost during walking while counting were presented ( $p>0.117$ ) (Table 20).

*Table 20: Dual task performance and dual task costs between groups*

Parameter	Healthy older adults	Persons with PD	t-value (df)	p-value
DT performance	3.73±0.15	2.98±0.11	2.48 (31)	<b>0.019</b>
DT cost on gait speed S3* (%)	3.54±2.69	22.78±2.87	-4.89 (30)	<b>&lt;0.001</b>
DT cost on stride length S3* (%)	-0.88±1.28	14.54±2.54	-5.69 (31)	<b>&lt;0.001</b>
DT cost on gait speed count** (%)	6.79±3.42	10.36±3.6	-0.71 (29)	0.486
DT cost on stride length count** (%)	2.84±1.56	-1.45±2.26	1.61 (29)	0.117

DT=dual task, \*S3=walking while subtracting 3s, \*\*count=walking while counting

No correlations between HbO<sub>2</sub> levels and DT performance and DT cost were found in persons with PD. However, in healthy older adults, higher HbO<sub>2</sub> level was inverse correlated with DT performance ( $r=-0.674$ ,  $p=0.002$ ), and dual task cost on gait speed was inversely correlated with DT performance ( $r=-0.674$ ,  $p=0.002$ ). In other words, subjects with high DT performance had lower DT cost on gait speed and lower level of HbO<sub>2</sub>.

#### 4.3.7 Summary objective 1

The brain regions activated during imagined walking in both, healthy older adults and persons with PD includes areas in the occipital, parietal, frontal, and cerebellum lobes. Between group comparisons revealed that persons with PD demonstrate higher activation during imagined usual walking and walking while negotiating obstacles while healthy older adults show higher activation during imagined walking while navigating. Within group comparisons demonstrate that healthy older adults increase activation during complex imagined walking situations as negotiating obstacles and navigating, compare to imagine usual walking. In contrast, persons with PD demonstrate increased brain activation only between imagined walking while negotiating obstacles and imagined usual walking. No changes in activation were observed between imagined walking while navigating and imagined usual walking.

Looking specifically at the frontal lobe during real walking revealed that the frontal lobe play important role during walking in complex situations in healthy older adults and persons with PD. However, in persons with PD, increased frontal activation was not seen during DT walking. Lower DT performance in persons with PD may provide possible explanation.

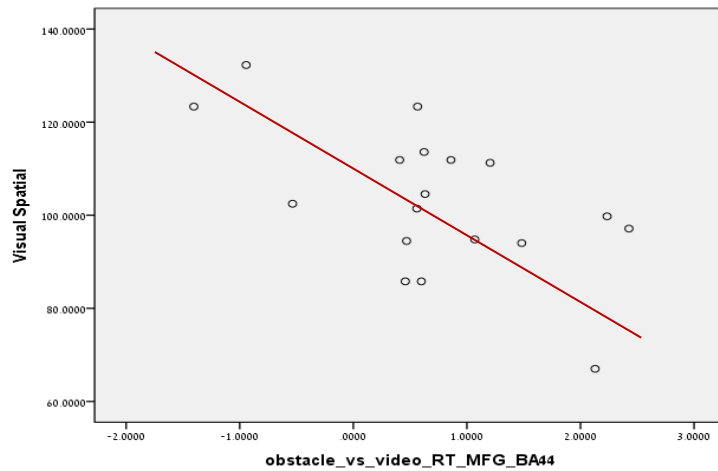
#### 4.4 Objective 2:

To assess the correlation between cognitive abilities and neural activation during imagined walking, a battery of computerized cognitive tests and neuropsychological tests were performed. The

neuropsychological tests included the TMT, while the computerized tests included tests as the Stroop and GoNoGo from which six scores were generated (1) general cognitive score (GCS), (2) memory, (3) executive function, (4) attention, (5) visual-spatial, and (6) information processing. The scores in these cognitive tests were correlated with level of activation in different regions of interest (ROI) in the frontal (SMA and BA 44), parietal (SPL) and cerebellum lobes during three imagined walking tasks; usual walking, walking while negotiating obstacles, and walking while navigating. These ROIs were extracted from a meta-analysis of motor imagery (Hetu et al., 2013).

#### 4.4.1 Healthy older adults

Inverse correlation was demonstrated between visual spatial score obtained from the computerized test and activation of right BA 44 (MFG) during imagined walking while negotiating obstacles ( $r=-0.592, p=0.010$ ) (Figure 26). In addition, inverse correlation was shown between information processing score obtained from the computerized test and activation of left SPL during imagined usual walk ( $r=-0.489, p=-0.00$ ). Inverse correlation between cognitive scores and ROIs activation indicates that in healthy older adults higher cognitive scores in the computerized tests are associated with lower activation in ROIs during imagined walking. No more correlations were found between cognitive scores and ROI activation in healthy older adults.



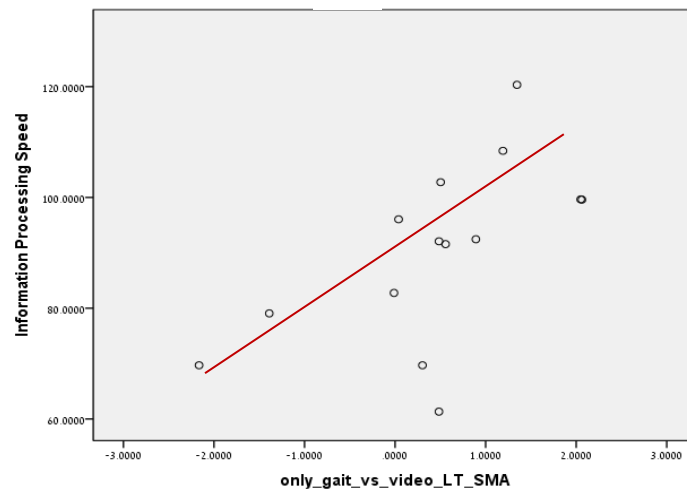
**Figure 25:** Inverse correlation between visual spatial score and RT MFG in healthy older adults

#### 4.4.2 Persons with PD

Direct correlations were found between cognitive scores and level of activation in SMA and BA 44 in the frontal lobe, and bilateral SPL in persons with PD. No correlations were demonstrated between cognitive scores and cerebellum. Table 21 presents the correlations between the cognitive scores and activation of ROIs during the imagined walking tasks. Higher scores in the computerized tests reflect better performance and higher cognitive abilities. In contrast, lower score in the TMT test reflect better performance and higher cognitive ability as it reflect time in seconds to complete the task. The observed correlations reveal that persons with PD with higher cognitive abilities are associated with higher activation of frontal and parietal regions (Figure 27).

*Table 21: The correlations between cognitive measurements and ROI activation in persons with PD*

ROI	Cog	MRI task					
		Usual walk		Obstacle walk		Navigation walk	
		Pearson (r)	P-value	Pearson (r)	P-value	Pearson (r)	P-value
LT	GCS	-	-	-	-	0.557	0.025
SMA	EF	0.543	0.030	0.534	0.033	-	-
	Inf	0.610	0.020	0.600	0.023	-	-
	TMT B	-0.681	0.005	-0.519	0.047	-	-
RT	GCS	0.504	0.047	-	-	-	-
BA	EF	-	-	0.560	0.024	-	-
44	Inf	0.659	0.010	0.597	0.024	-	-
	TMT B	-0.582	0.023	-	-	-	-
RT	EF	-	-	-	-	0.685	0.003
SPL	Inf	-	-	0.616	0.019	-	-
	TMT B	-0.582	0.023	-	-	-	-
LT	Inf	-	-	0.599	0.024	-	-
SPL	TMT B	-0.575	0.025	-	-	-	-

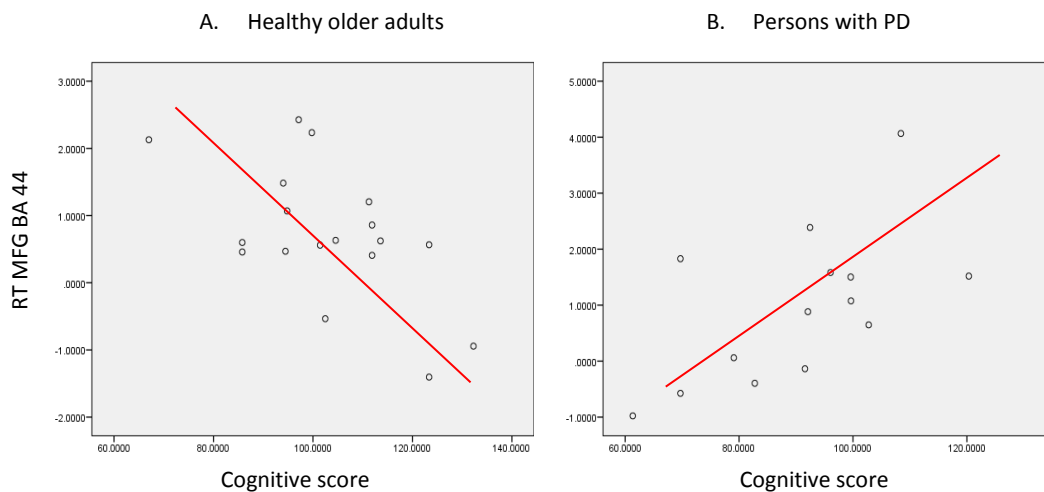


**Figure 26:** Correlation between information processing score and activation of LT SMA in persons with PD



#### 4.4.3 Persons with PD compared to healthy older adults

According to the results the correlation between cognitive abilities and neural activation during imagined walking differ between healthy older adults and persons with PD. While healthy older adults with high cognitive abilities demonstrate lower activation in MFG and SPL, persons with PD with high cognitive abilities show higher activation in frontal and parietal areas.



**Figure 27:** Different correlations between brain activation and cognitive performance in healthy older adults and persons with PD

*Changes in MFG BA 44 activation during imagined walking while negotiating obstacles as function of performance in cognitive tests in healthy older adults and persons with PD. **Figure 28A** represent the inverse correlation between brain activation and cognitive performance in healthy older adults. As shown, higher scores on the cognitive tests (high performance) are associated with reduced brain activation suggesting that efficiency promote activation. In contrast, **Figure 28B** represents the direct correlation between brain activation and cognitive performance in persons with PD. As shown, higher scores on cognitive tests are associated with increased brain activation suggesting that compensatory strategies are activated to allow performance.*

#### 4.5 Objective 3

To assess the correlations between motor performance of walking in complex situations and neural activation during imagined walking we suggested two parameters: (1) distance of feet from obstacle and (2) dual task cost. However, difficulties in attaining accurate measurements of distance of feet from obstacle did not allow us to use it to assess motor performance. As such, dual task cost and scores in mobility tests were used to assess motor performance. Dual task cost was assessed based on gait speed and stride length, and mobility tests comprised the FSST and 2MWT. These measurements were correlated with level of activation in different regions of interest (ROI) in the frontal, parietal and cerebellum lobes during three imagined walking tasks; usual walking, walking while negotiating obstacles, and walking while navigating. These ROIs were extracted from a meta-analysis of motor imagery (Hetu et al., 2013).

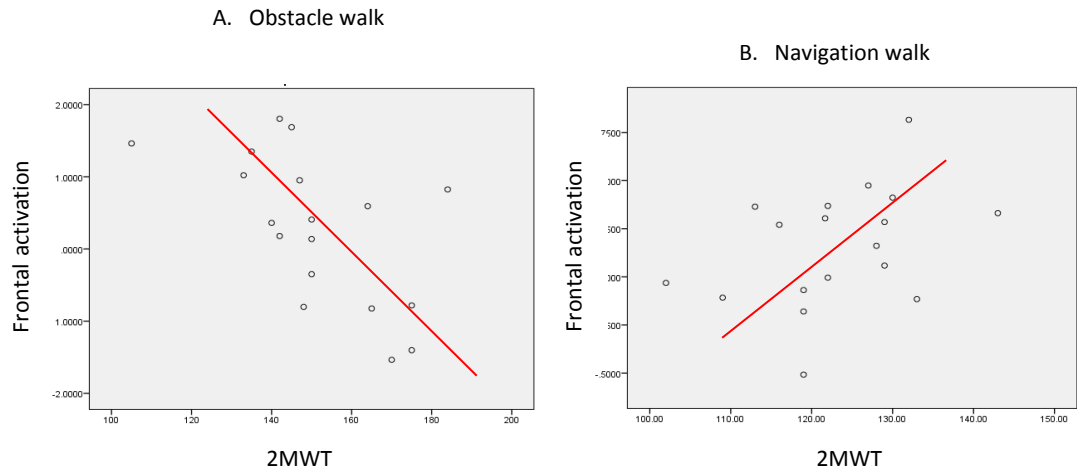
##### 4.5.1 Healthy older adults

No correlations were found between motor performance and brain activation during imagined usual walking. Inverse correlations were shown between motor performance and brain activation during imagined walking while negotiating obstacles. In contrast, positive correlations were presented between motor performance and activation during walking while navigating (Table 22 and Figure 29). Note that higher score on 2MWT indicates better performance while lower score on FSST and DT cost indicates better performance.

*Table 22: The correlation between motor performance and ROI activation in healthy older adults*

ROI	Mobility	MRI task					
		Usual walk		Obstacle walk		Navigation walk	
		r	p	r	p	r	p
LT	FSST	-	-	-	-	-0.565	0.015
SMA	2MWT	-	-	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-0.498	0.042
	DT cost stride <sup>b</sup>	-	-	-	-	-	-
RT	FSST	-	-	-	-	-	-
SMA	2MWT	-	-	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-	-	-0.472	0.048
LT	FSST	-	-	-	-	-	-
IFG	2MWT	-	-	-	-	0.552	0.018
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-	-	-0.631	0.005
RT	FSST	-	-	0.470	0.049	-	-
IFG	2MWT	-	-	-0.601	0.008	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-	-	-	-
RT	FSST	-	-	-	-	-	-
SPL	2MWT	-	-	-0.583	0.011	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-	-	-	-
LT	FSST	-	-	-	-	-0.479	0.044
IPL	2MWT	-	-	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-0.586	0.014
	DT cost stride <sup>b</sup>	-	-	-	-	-	-

<sup>a</sup>=DT cost on gait speed, <sup>b</sup>=DT cost on stride length



**Figure 28:** Changes in frontal activation during imagined obstacle walking and navigation walking as function of performance in 2 minute walking test

Figure 29A represents the inverse correlations between frontal activation during obstacle walking and performance on 2MWT and Figure 29B reveal the positive correlation between frontal activation during walking while navigating and 2MWT in healthy older adults.

#### 4.5.2 Persons with PD

Better performance on the mobility tests and lower DT cost correlated with higher brain activation (Figure 27) during imagined usual and obstacle negotiation walking in SMA and IFG, and bilateral SPL in persons with PD. No correlations were demonstrated between motor performance and cerebellum. In addition, no correlations were found between motor performance and brain activation during imagined walking while navigating. Table 23 presents the correlations between motor performance and activation of ROIs during the different imagined walking tasks.

Table 23: The correlation between motor performance and ROI activation in persons with PD

ROI	Motor performance	MRI task					
		Usual task		Obstacle walk		Navigation	
		r	p	r	p	r	p
LT	FSST	-0.733	0.002	-0.672	0.006	-	-
SMA	2MWT	0.574	0.025	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-0.550	0.033	-	-	-	-
RT	FSST	-0.551	0.033	-0.604	0.017	-	-
SMA	2MWT	0.535	0.040	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-	-	-	-
LT	FSST	-0.692	0.004	-0.699	0.004	-	-
IFG	2MWT	0.590	0.021	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-0.571	0.026	-	-
RT	FSST	-	-	-0.672	0.006	-	-
IFG	2MWT	-	-	-	-	-	-
	DT cost speed <sup>a</sup>	-0.680	0.005	-	-	-	-
	DT cost stride <sup>b</sup>	-0.604	0.017	-	-	-	-
RT	FSST	-0.692	0.004	-0.852	<0.001	-	-
SPL	2MWT	0.538	0.039	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-	-	-	-
LT	FSST	-	-	-0.608	0.016	-	-
IPL	2MWT	-	-	-	-	-	-
	DT cost speed <sup>a</sup>	-	-	-	-	-	-
	DT cost stride <sup>b</sup>	-	-	-	-	-	-

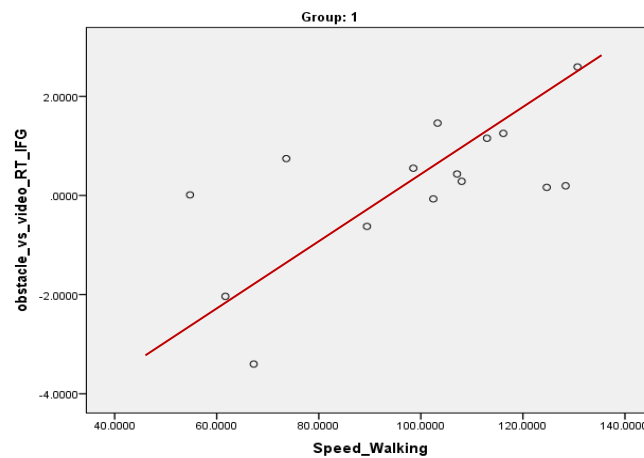


Figure 30: Correlation between dual task cost on walking speed and frontal activation in persons with PD

#### 4.5.3 Persons with PD compared to healthy older adults

According to these results the correlation between motor performance and neural activation during imagined walking differ between healthy older adults and persons with PD. While during imagined usual and obstacle negotiation walking healthy older adults with better motor performance demonstrated lower activation in middle frontal gyrus and SPL, persons with PD with better motor performance show higher activation in frontal and parietal areas. However, during imagined walking while navigating no correlations between motor performance and brain activation were observed in persons with PD while in healthy older adults the pattern of activation was changed and better performance was correlated with increased activation.

##### 4.5.3.1 Summary:

Correlations between the scores obtained from the different tests (cognitive and motor performance) and neural activation during imagined walking demonstrate different activation pattern between healthy older adults and persons with PD. Healthy older adults with better performance demonstrate decrease neural activation while persons with PD that performed better show increase in neural activation. This increase activation in persons with PD may be a compensatory strategy to enable performance.

#### 4.6 Objective 4:

To predict the performance of walking in complex situations by the mobility tests, performance of walking was defined as the dual task cost on

gait speed and stride length. As indicated, we were not able to use the distance of feet from obstacle to define motor performance of walking while negotiating obstacles due to difficulties in obtaining accurate measurements. The scores in the three mobility tests: FSST, MiniBEST, and 2MWT (description of the tests is provided in section 3.2 page 68) were used to predict the dual task cost.

#### 4.6.1 Healthy older adults

The three mobility tests significantly predicted dual task cost on gait speed, and explained 78.8% of variance in the dual task cost. However, they did not predict dual task cost on stride length (Table 24).

*Table 24: Linear regression for healthy older adults*

Dual task cost	Mobility test	R	R <sup>2</sup>	Beta	t-test	p-value
Gait speed	FSST	0.800	0.640	0.476	3.027	<b>0.008</b>
	MiniBEST	0.831	0.690	0.262	2.073	<b>0.056</b>
	2MWT	0.887	0.788	0.394	2.625	<b>0.019</b>
Stride length	FSST	0.665	0.442	0.455	1.91	0.074
	MiniBEST	0.672	0.451	0.116	0.614	0.548
	2MWT	0.705	0.497	0.274	1.205	0.246

#### 4.6.2 Persons with PD

The mobility tests did not predict dual task cost on gait speed ( $p>0.121$ ) and dual task cost on stride length ( $p>0.125$ ) in persons with PD.

## 5 DISCUSSION

The aim of this study was to define the underlying brain mechanisms of walking in complex situations in healthy older adults and persons with PD. For this purpose, three imagined walking tasks with different cognitive and motor loads were conducted using fMRI. In this chapter, the fMRI findings will be discussed based on three contrasts that were performed:

- (1) Comparison between imagined usual walking in a virtual scene and watching the same virtual scene.
- (2) Comparison between imagined walking while negotiating obstacles and imagined usual walking.
- (3) Comparison between imagined walking while navigating and imagined usual walking.

In addition, we will discuss the correlations between brain activation and motor-cognitive performance. Brain activation was defined according to the activation in frontal ROIs extracted from a meta-analysis of motor imagery (Hetu et al., 2013) during each of the imagined walking tasks.

In order to better understand our findings in the context of walking, we used fNIRS to allow monitoring frontal activation during real walking. Similar to the fMRI protocol, the fNIRS protocol comprised different walking tasks with graded cognitive and motor loads. fNIRS findings will be discussed in the light of three issues:

- (1) Usual walking vs. dual task walking



- (2) Walking with motor vs. cognitive load (obstacle vs. subtracting 3s)
- (3) Walking with simple vs. complex cognitive load (counting forward vs. subtracting 3s).

### 5.1 The neural mechanisms underlying imagined walking

Comparison between imagined usual walking in a virtual scene and watching the same virtual scene takes into account brain activation associated with vision. Therefore, this contrast allow us to measure brain activation related specifically to motor imagery of walking. In both groups this contrast showed increased activation in large brain areas that encompass frontal, parietal, occipital, and cerebellum regions during motor imagery of gait. These results are in line with the literature suggesting that imagined walking is associated with the planning and preparation phases of actual gait (Grezes & Decety, 2001; Hetu et al., 2013; Holmes & Calmels, 2008; Zacks, 2008). The observed frontal activation may be related to motor planning and cognitive aspects of imagined walking (Holtzer, Epstein, Mahoney, Izzetoglu, & Blumen, 2014; Hoshi & Tanji, 2007), and the parietal activation may be connected with integration of multisensory inputs required to create movement representation (Fogassi & Luppino, 2005; Torres, Raymer, Gonzalez Rothi, Heilman, & Poizner, 2010). Occipital activation is associated with the visual-spatial aspects of motor imagery of gait (Zeki et al., 1991), and activation of the cerebellum is likely related to its role in motor control (Thach, 1998). This pattern of

activation across various brain structures allows us to discuss the underlying mechanism of imagined walking in terms of neural networks.

The neural networks associated with motor imagery have been discussed in a recent meta-analysis that reviewed 75 articles (Hetu et al., 2013). Our findings are in line with the results of this meta-analysis which reported activation in fronto-parietal networks, cerebellum, and subcortical regions (Hetu et al., 2013). In contrast, we also found activation in the visuo-occipital network that encompasses large occipital areas such as BA 18 and 19. The activation of this network in our study may be the result of using virtual reality in which persons with PD were asked to imagine themselves walking. In contrast, many of the studies in the meta-analysis performed motor imagery with eyes closed or presented a static picture. Iseki et al used video clips to induce imagery of walking and also showed increase activation in right and left middle occipital gyrus, BA 18 and 19 (Iseki, Hanakawa, Shinozaki, Nankaku, & Fukuyama, 2008). It is possible that such effects are related to optical flow of observing the VR scene. Another possible explanation relates to the methodology of the fMRI analysis used in the studies in the meta-analysis. In most studies ROI analysis that did not include occipital regions were performed. For example, similar to our study, Shine et al. also showed a virtual reality scene, however, the analysis focused on five specific neural networks that did not include the occipital lobe (Shine et al., 2013). Interestingly, occipital activation in our study was observed while watching the virtual scene while this activation was absent when persons with PD watched a static picture.

This suggests that the moving images on the screen elicited activation that may relate to visual processing (Snijders et al., 2011). In order to better understand the role of each neural network in the performance of imagined usual walking, each neural network will be discussed separately.

### 5.1.1 Fronto-parietal network

The network associated with motor imagery is the fronto-parietal network (Hetu et al., 2013; Holtzer et al., 2014; Hoshi & Tanji, 2007). In line with the literature, our findings show three frontal regions and two parietal regions that were more activated during motor imagery of gait than during only watching. The frontal regions include: (1) premotor cortex (PMC), (2) dorsolateral and medial prefrontal cortex (DLPFC), and (3) inferior frontal gyrus (IFG), and the parietal regions include: (1) inferior parietal lobule (IPL) and (2) superior parietal lobule (SPL) (Tables 7 and 8).

#### 5.1.1.1 Premotor cortex

One frontal region involved in motor imagery is the premotor cortex. Studies have shown that premotor regions play an important role in the planning, preparation and execution of motor actions (Hoshi & Tanji, 2007). Premotor regions that are activated during motor imagery include the MFG and SMA (Hetu et al., 2013; Hoshi & Tanji, 2007; Zacks, 2008). The consistent activation of SMA during motor imagery shown in the literature could be related to the processing of complex information associated with movement and visuo-spatial transformation (Leek &

Johnston, 2009). The exact nature of the role of the SMA may depend on methodological variables such as the control condition that was used.

In our study, imagined walking elicited activation in bilateral BA 6, which consists of the premotor cortex however, specific SMA activation was not observed. The reason may be related to the control condition. While in the meta-analysis most of the studies used rest or fixation in this study persons with PD watched videos as the control condition. The SMA may be involved in visuo-spatial transformation leading to activation already while only watching a video (Leek & Johnston, 2009). Thus, it is possible that SMA activation during the control condition of watching a video was counterbalanced with the activation during imagined task. Another explanation may be related to the analysis that were performed. Smoothing with small kernel as part of the preprocessing and conducting whole brain analysis with cluster size of 10 voxels may mask possible activation in the SMA. Further ROI analysis that includes the SMA may reveal specific activation associated with motor imagery of walking.

#### 5.1.1.2 Dorso-lateral pre-frontal cortex (DLPFC)

A second frontal region involved in motor imagery is the DLPFC that lies in the middle frontal gyrus (MFG) and is attributed anatomically to BA 8, BA 9, BA 10, and BA 46. The DLPFC plays an important role in executive functions, such as working memory, cognitive flexibility, inhibition (Deary, Penke, & Johnson, 2010; Owen, McMillan, Laird, & Bullmore, 2005; Wager, Jonides, & Reading, 2004), motor planning,

organization, and regulation (Harding, Yucel, Harrison, Pantelis, & Breakspear, 2015). Similar to the reported findings from the literature, we found increased activation in BA 9 and BA 8 during imagined usual walking, compared to watching (Hetu et al., 2013; Holtzer et al., 2014) (Tables 7 and 8). Although it is well known that the DLPFC plays an important role during walking, a PET study that compared real walking to imagined walking reported that DLPFC is more activated during motor imagery of walking than during real walking (la et al., 2010). This increased activation during imagined walking suggests that motor imagery of walking possess higher cognitive demands associated with attention, executive function, and motor planning than real walking. It is important to keep this in mind as our results showed lower cognitive scores in persons with PD, compared to the healthy controls (Table 5).

#### 5.1.1.3 Inferior frontal gyrus (IFG)

A third frontal region involved in motor imagery is the inferior frontal gyrus (IFG) mainly BA 44. Our results show that there is activation in bilateral IFG during imagined usual walking in both healthy older adults and persons with PD (Tables 7 and 8). This activation may be related to the suppressed execution of real movements during the imagined walking tasks and/or the detection of relevant cues in the virtual reality scene that enhance the imagined walking. BA 44 is mostly known as part of Broca's area, a region involved in semantic tasks, however, recent studies show that the left BA 44 is involved in inhibitory control and more generally in the detection of salient or task relevant cues (Hampshire, Chamberlain, Monti,

Duncan, & Owen, 2010). Hampshire et al. reported that the right IFG is recruited when important cues are detected, regardless of whether that detection is followed by the inhibition of a motor response, the generation of a motor response, or no external response (Hampshire et al., 2010).

#### 5.1.1.4 Parietal cortex

The parietal cortex is an important sensory integration hub. Its different sub-regions project to various brain areas including the premotor cortex, and play an important role during motor execution (Fogassi & Luppino, 2005; Fogassi et al., 2005). Consistent with the literature, we find activation in the IPL and SPL corresponding to BA 7, BA 40 and precuneus (Tables 7 and 8). The parietal cortex is involved in four processes that are necessary to perform motor imagery: (1) code for the goals of actions (Fogassi et al., 2005; Tunik, Rice, Hamilton, & Grafton, 2007), (2) visuomotor transformation processes (Mutha, Sainburg, & Haaland, 2011; Torres et al., 2010), (3) motor attention processes (Rushworth, Johansen-Berg, Gobel, & Devlin, 2003), and (4) updating and maintaining postural representation.

The posterior parietal cortex (PPC) which includes the IPL and SPL is involved in visuo-motor transformation processes important in visually guided motor tasks (Mutha et al., 2011; Torres et al., 2010). This role of the PPC explains the activation in the present study, in which motor imagery of walking was visually guided by the virtual environment. The precuneus, part of the SPL that corresponds to BA 7, plays an important

role in a wide spectrum of highly integrated tasks involved in visuo-spatial imagery and visually guided motor tasks. This region is believed to be involved in visuo-spatial processing, reflections upon self, and aspects of consciousness (Mutha et al., 2011). Indeed, imagined walking would require the participant to access the goal of the movement, prepare the simulated walking and while imagining it, update its postural representations, functions that have been attributed to the parietal cortex (Fogassi et al., 2005; Torres et al., 2010; Tunik et al., 2007) . Table 25 summarizes the brain regions in the fronto-parietal network that were more activated during imagined walking, compared to watching, and their possible role in motor imagery of walking.

*Table 24 The brain regions in the fronto-parietal network and their role in motor imagery of gait in persons with PD and healthy older adults*

Lobe	structure	BA/region	Possible role
Frontal	MFG	BA6/SMA	Planning complex coordinated movements (Holtzer et al., 2014; Hoshi & Tanji, 2007)
		BA9/DLPFC	Executive function and attention (Kubler, Dixon, & Garavan, 2006; Shallice, Stuss, Alexander, Picton, & Derkzen, 2008)
	IFG	BA44/OFC	Inhibitory control, detection of relevant cues (Hampshire et al., 2010)
Parietal	SPL	BA7 / Precuneus	Sensory integration hub associated with motor coordination, visual guidance of an action, directing attention in space, shifting attention between motor targets (Mutha et al., 2011)
	IPL	BA40	Interpretation of sensory information (Gur et al., 2007; Singh-Curry & Husain, 2009)

BA=Brodmann area, MFG=middle frontal gyrus, SMA=supplementary motor area, DLPFC=dorso-lateral prefrontal cortex, IFG=inferior frontal gyrus, OFC= orbitofrontal cortex, SPL=superior parietal lobule, IPL=inferior parietal lobule

### 5.1.2 Visuo-occipital network

Cortical areas outside the fronto-parietal regions that were activated during imagined usual walking in both persons with PD and healthy older adults include occipital areas such as BA 18 and BA 19. These areas are considered to be part of the visuo-occipital cortex, in particular, the visual association area, that is responsible for feature-extraction, shape recognition, attentional, and multimodal integrating functions (Beauchamp et al., 2001; Blackwood et al., 2004; Luo, Niki, & Knoblich, 2006; Qiu et al., 2010). BA 18 is associated with the interpretation of images and BA 19 is sensitive to motion (Beauchamp et al., 2001; Lui, Bourne, & Rosa, 2006). Since we presented a video of a virtual environment to the patients to induce motor imagery of walking, it is not surprising that visual association areas that are sensitive to motion were activated. This is consistent with the findings of Fougere et al. They used PET-fMRI to compare real and imagined walking and observed activation in BA 18 and BA 19, during both real and imagined walking in healthy subjects (Ia et al., 2010). This increased activation indicates that visually guided spatial navigation is required for performing both real and imagined walking tasks. Table 26 summarizes the brain regions in the visuo-occipital network that were more activated during imagined walking, than watching, and their possible role in performing motor imagery of walking in both groups



*Table 25: The brain regions in visuo-occipital network and their role in motor imagery of gait in persons with PD and healthy older adults*

<b>Lobe</b>	<b>Structure</b>	<b>BA/region</b>	<b>Possible role</b>
Occipital	SOG	BA18 & 19	Visual association area responsible for feature-extraction, interpretation of images, visual attention and multimodal integrating functions (Zeki et al., 1991)
Temporal	MTG		Detection of biological motion (Hoshi & Tanji, 2007)

*BA= Brodmann area, SOG=superior occipital gyrus, MTG=middle temporal gyrus*

### 5.1.3 Cerebellum and subcortical regions

In line with the literature, we found increased activation in various parts of the cerebellum during imagined walking (Hetu et al., 2013; Holtzer et al., 2014). The cerebellum, through its connections to superior and inferior parietal cortex, is involved in the execution of various types of movement (Prevosto, Graf, & Ugolini, 2010). It receives input from sensory systems and other parts of the brain, and integrates these inputs to fine tune motor activity (Prevosto et al., 2010; Prevosto & Sommer, 2013). The cerebellum contributes to the accuracy of movement, equilibrium and posture, and is a major player in motor control and motor learning (Manto et al., 2012; Manto & Oulad Ben, 2013). Giving all these functions of the cerebellum during movement execution, its activation during imagined walking is not surprising.

In contrast to the literature we did not find significant activation in subcortical regions as the putamen and caudate nucleus during imagined usual walking. The performance of whole brain analysis at cluster size of 10 voxels may explain these discrepancies. Since the total size of subcortical structures is relatively small, increased activation may not pass multiple comparisons tests. In order to better understand the specific role of subcortical regions during imagined walking and the differences in activation between persons with PD and healthy older adults, region of interest analysis (ROI) that include regions in the basal ganglia should be conducted.

An additional explanation for not observing changes in activation may be related to the specific role the basal ganglia play as intrinsic pacer during movement (Plenz & Kital, 1999). It is possible that the virtual reality simulation used in this study to enhance motor imagery of gait acted as an extrinsic pacer which provided a consistent rhythm. This extrinsic rhythm helped to initiate the imagined walking at a certain pace during the task and reduced the need for activation of subcortical structures. Table 27 summarizes the regions in the cerebellum and subcortical nucleus that were more activated during imagined walking and their possible role in performing motor imagery of walking.

*Table 26: Cerebellum and subcortical regions and their role in motor imagery of gait in persons with PD and healthy older adults*

Structure	Region	Possible role
Cerebellum	Posterior	Fine motor coordination, inhibition of involuntary movement (Glickstein & Doron, 2008; Koziol et al., 2014)
	Anterior	Unconscious proprioception (Glickstein & Doron, 2008; Koziol et al., 2014)
Subcortical	Putamen	Motor preparation, movement selection, movement sequences and rhythm, motor learning (Marchand et al., 2008; Plenz & Kital, 1999)
	Thalamus	Hub of information, processes necessary data for motor control (Bosch-Bouju, Hyland, & Parr-Brownlie, 2013)

#### 5.1.4 Comparison between healthy older adults and persons with PD

Similar brain regions were activated during imagined usual walking in healthy older adults and persons with PD. However, persons with PD activated the visuo-occipital cortex and the frontal-parietal network more than healthy older adults. These findings are in line with a recent study by Wai et al. suggesting that the visuo-motor pathway is not altered by the PD pathology. Still, more visuo-spatial resources are required to complete the same task in persons with PD, as compared to age matched healthy older adults. Taken together, our findings show that persons with PD activate similar brain regions as healthy older adults but to a greater extent, suggesting an inefficient brain activation that require compensatory mechanisms.

### 5.1.5 Summary of findings in relation to hypothesis

The activation of the fronto-parietal network confirms our first hypothesis (section 1.5). Imagined walking apparently requires the activation of frontal and parietal regions that are part of the fronto-parietal network in both groups. However, in contrast to our hypothesis, activation of the visuo-occipital network was already found during imagined usual walking and not just during imagined walking while negotiating obstacles. One possible explanation is the high visual processing demands associated with the use of virtual reality simulation.

In addition, we observed increased activation in fronto-parital and visuo-occipital networks in persons with PD, compared to healthy older adults. This supports our hypothesis. We had postulated that persons with PD would demonstrate inefficient activation that require compensatory strategies to perform imagined usual walking.

## 5.2 Differences in neural mechanisms underlying imagined walking while negotiating obstacles and imagined usual walking

The similar visual stimulation in the two imagined tasks counterbalance visual activation related to the virtual scene. Comparison between imagined walking while negotiating obstacles and imagined usual walking showed increased activation in middle frontal gyrus (MFG), middle occipital gyrus (MOG), and cerebellum during imagined walking while negotiating obstacles in both groups (section 4.3.4 page 113). The greater

activation in these brain regions relates to the higher demands this task of imagined obstacle negotiation poses on the visuo-motor network.

These findings are consistent with the literature (Wagner et al., 2008; Wai et al., 2012; Wang et al., 2009). As mentioned (Table 25), increased activation in MFG may be related to the higher attention and motor planning demands an imagined stepping over obstacle movement requires (Holtzer et al., 2014; Hoshi & Tanji, 2007). The increased activation in MOG is associated with the higher visual-spatial demands the moving obstacles in the scene poses (Table 26). Increased activation in the cerebellum is related to higher level of fine motor coordination and proprioception the task of imagined stepping over obstacle requires (Table 27). However, increased activation in the precuneus during imagined walking while negotiating obstacles was observed only in healthy older adults (Table 10). No differences in parietal activation between tasks were observed in persons with PD. This inability to increase activation in parietal regions during a more complex task provide evidence to the reduced capacity and limited resources in persons with PD, which can be explained by the capacity sharing theory. According to this theory, when more than one task is performed there is less capacity for each individual task. Less capacity impaired the performance of the tasks and make the tasks more difficult. Since we were not able to assess the performance of imagined walking while negotiating obstacles, the functional consequences of inability to increase activation in parietal regions is unknown. Although activation in frontal, occipital and cerebellum regions were observed in

both groups, the extent of activation differ between the groups, showing higher activation in persons with PD.

#### 5.2.1 Comparison between healthy older adults and persons with PD

A comparison between the two groups showed significant increased activation in right frontal and left occipital regions in persons with PD (Table 12). This increased activation may be associated with the higher planning and attentional demands this condition poses on persons with PD compared to healthy older adults. Lateralization of the frontal lobe has been investigated in the literature, indicating asymmetrical organization of verbal and spatial working memory. Verbal storage tasks have been associated with a predominance of left-hemisphere activation in Broca's area, supplementary motor cortex, premotor cortex, and superior and inferior parietal cortex (Jonides, Smith, Marshuetz, Koeppel, & Reuter-Lorenz, 1998; Schumacher et al., 1996). In contrast, spatial storage tasks have been associated with predominance activation in right-hemisphere regions homologous to those active during verbal storage, and visual association cortex (Awh, Jonides, & Reuter-Lorenz, 1998; Fiez et al., 1996; Jonides et al., 1998; Schumacher et al., 1996). The increased activation in persons with PD specifically in right frontal regions may indicate that imagined walking while negotiating obstacles requires spatial storage.

In contrast, increased activation in visuo-occipital cortex was seen specifically in the left hemisphere. These findings are in line with Wai et al. who demonstrated increased activation in left middle occipital gyrus corresponding to BA 19 and left cuneus corresponding to BA 18 in persons with PD during motor imagery of gait (Wai et al., 2012). Specific activation of the left occipital association area was previously attributed to the function of judging the dimensions of different patterns in space (Kosslyn et al., 1999). Giving this specific role of left visual association areas, the increased activation we observed in left middle occipital gyrus may be related to the visuo-spatial deficits shown in persons with PD (Galna et al., 2012). Due to these deficits persons with PD put more effort in estimating the dimensions of the obstacles and in planning their steps and strategy.

The analyses were performed at a group level in which the results presented the average brain activation of all subjects within each group. Inclusion criteria for persons with PD was H&Y II-III which by definition includes wide range of subjects that manifest different levels of cognitive and motor deficits. Perhaps, persons with PD that mainly presented motor deficits, activated different brain regions than persons with more cognitive impairments. Better understanding of the differences in brain activation between subgroups of persons with PD may have important implications on the type of intervention that should be provided.

### 5.2.2 Summary of findings in relation to hypothesis

The activation of fronto-parital and visuo-occipital networks in both groups during imagined walking while negotiating obstacle supports our hypothesis. In addition, higher activation of visuo-occipital network in persons with PD compare to healthy older adults support our hypothesis.

### 5.3 Differences in neural mechanisms underlying imagined walking while navigating and imagined usual walking

Comparison between imagined walking while navigating and imagined usual walking revealed increased activation in right parietal and bilateral occipital lobes during imagined walking while navigating in healthy older adults. Occipital activation, specifically in BA 18 and BA 19, is associated with visuo-spatial processes that are required to visualize the route while performing the imagined walking task. Parietal regions as the precuneus and BA 7, integrate the various motor-cognitive functions associated with the performance of imagined walking while navigating. These findings are in line with number of studies that showed activation in parietal regions such as SPL and IPL, and visuo-occipital networks while performing spatial cognition tasks, for example, navigation through a virtual labyrinth (Jordan et al., 2004; Zhang et al., 2012).

In contrast to healthy older adults, no differences in activation between imagined walking while navigating and imagined usual walking



were observed in persons with PD. In the navigation task, we were able to assess the performance based on the correct and incorrect turns made by pressing on the response box. Evaluation of this task performance revealed that in healthy older adults 90% of the responses were correct while in persons with PD only 53% were correct, slight higher than above chance.

The low performance in the navigating task and the unchanged activation during the performance of imagined walking while navigating in persons with PD can be explained by both the capacity sharing and bottleneck theories (Pashler, 1994; Wu & Hallett, 2008). As shown before increased activation across all brain regions occurred already during imagined usual walking. This increased activation during usual walking reflect a ceiling effect which demonstrate the limited brain reserves available for more complex task as imagined walking while navigating. In addition, motor imagery is a mental task associated with activation of DLPFC. When viewed as dual tasks, an alternative explanation to the low performance is the bottleneck theory (Pashler, 1994; Wu & Hallett, 2008). According to this theory, parallel processing of tasks that utilized the same networks may be lead to interference for certain mental operations. Perhaps the impaired cognitive system of persons with PD requires a single mechanism to be dedicated to each one of these tasks, imagined walking and navigating through memorized route, for some period of time. Therefore, when the two tasks compete for the same networks at the same time, a bottleneck results, and one or both tasks are impaired.

### 5.3.1 Comparison between healthy older adults and persons with PD

A priori, the task of imagined walking while navigating has the highest cognitive load, among the different tasks that we studied, as it is associated with route planning and memorization. The low performance among the persons with PD suggests that they could not meet the high cognitive demands of this task. According to the cognitive tests that were conducted as part of the assessment, the persons with PD had significantly lower cognitive scores on all computerized cognitive tests and neuropsychological tests (Table 5). These lower cognitive abilities may explain the difficulties persons with PD encountered while performing imagined walking while navigating.

In healthy older adults our findings revealed specific activation in frontal, limbic, and insula regions (Table 13). Frontal areas included the SMA that plays an important role in motor planning (Hetu et al., 2013; Zacks, 2008), and BA 9 and BA 10 which are important contributors in executive function (Hetu et al., 2013; Hoshi & Tanji, 2007). Limbic areas included the anterior cingulate cortex (ACC) corresponding to BA 24 and BA 32, both associated with cognitive functions, such as decision-making (Rushworth, Walton, Kennerley, & Bannerman, 2004; Wallis & Kennerley, 2011). The ACC is involved in error detection and in eliciting correct response (Fan, Hof, Guise, Fossella, & Posner, 2008). Its role in monitoring of conflict was also put forward showing that upon detection of a conflict, such as approaching an intersection in the virtual environment,

the ACC provides cues to other areas in the brain to cope with the conflicting control systems (Carter & van, V, 2007; Mansouri, Tanaka, & Buckley, 2009). The insula is implicated in large number of widely different functions, among them various cognitive functions that probably contribute to the performance of motor imagery and navigation.

Learning spatial properties of the surrounding environments can be achieved by directly navigating it or by studying it from a map. During map learning, one can visualize the relation of objects and landmarks in an environment from a single overview perspective, and then use it to derive paths to reach the target. In our study, subjects were required to learn a specific route by showing a map. However, after learning the map, subjects were presented a virtual scene of a landscape in which they were asked to imagine themselves walking according to the route that was learned. As such, this task combines these two forms of “route learning”.

Zhang H et al. [83] compared between the recruitment of brain networks during these two forms of route learning in healthy subjects. During map learning, they observed activation in the frontal, temporal, occipital, cingulate and insula areas. In contrast, during navigating through a virtual environment, there was increased activation in areas such as parietal and retrosplenial areas (Zhang et al., 2012). As specified above, in our study, healthy older adults presented increased activation in frontal and limbic regions during imagined walking while navigating (Table 13). This activation may indicate that healthy older adults relied on the

presented map while performing the imagined walking in the virtual scene as was instructed.

It is important to note that in contrast to the literature in which subjects were instructed to navigate in a labyrinth, in our study subjects were additionally required to imagine themselves walking while memorizing the planned route. These multiple cognitive tasks performed simultaneously may have increased the cognitive load on the system

### 5.3.2 Summary of findings in relation to hypothesis

The increased activation in fronto-parital network and limbic regions during imagined walking while navigating in healthy older adults confirmed our first hypothesis. However, this was not confirmed in persons with PD that showed no differences in brain activation between navigating walk and usual walk. The inability of persons with PD to increase brain activation during a more complex task as walking while navigating was associated with low performance.

#### 5.4 Correlation between brain activation and motor-cognitive performance

Brain activation in each of the imagined walking tasks demonstrated different correlations with the scores in motor-cognitive tests. In addition, different correlations were observed between the two groups. In healthy older adults we found: (1) no correlations between brain activation during usual walk and motor-cognitive performance, (2) inverse correlations between brain activation during obstacle walk and motor-cognitive performance, and (3) positive correlations between brain activation during navigating walk and motor-cognitive performance (Table 22). However, in persons with PD we revealed: (1) positive correlations between brain activation during usual walk and motor-cognitive performance, (2) positive correlations between brain activation during obstacle walk and motor-cognitive performance, and (3) no correlations between brain activation during navigating walk and motor-cognitive performance.

No correlations between brain activation during usual walk and motor-cognitive performance in healthy older adults may indicate that this task require low level of brain activation. However, no correlations between brain activation during navigating walk and motor-cognitive performance in persons with PD may reflect their limited ability to perform the navigating walk task. Additionally, it may explains why scores in mobility tests could not predict performance of complex walking in persons with PD (Table 24).

In healthy older adults the positive correlations shown during navigating walk were in contrast to the inverse correlations shown during walking while negotiating obstacles (Table 22). These findings suggest that in healthy older adults the demands of a task may change the strategy used to direct pattern of brain activation. While during imagined walking while negotiating obstacles efficiency is promoted, during imagined walking while navigating subjects increased activation to allow performance (Figure 29). These results show that task difficulty play a role in directing the brain activation strategy in healthy older adults. However, this study design can partially explain the relationship between brain activation strategy and task difficulty. This can be fully understood by performing a task in which difficulty is increased gradually.

Interestingly, opposite correlations between brain activation during obstacle walk and motor-cognitive performance were observed between the two groups. Healthy older adults demonstrated inverse correlations, while persons with PD presented positive correlations (Tables 21-23). These results suggest that each group used a different brain activation strategy to perform the imagined walking tasks. Healthy older adults utilized strategies that promote efficiency till certain degree of task difficulty, in which the performance of the task was at the expense of efficiency. In contrast, in persons with PD, the ability to perform the task was at the expense of efficiency already during simple task as imagined usual walk.

The positive correlations between brain activation during imagined walking while navigating and motor-cognitive performance in healthy older adults, and the positive correlations between brain activation during imagined usual and obstacle walking and motor cognitive performance in patients with PD, are in contrast to our second and third hypotheses.

## 5.5 Frontal brain activation during real walking tasks measured with the fNIRS

Five tasks, four walking tasks and one standing task, were included in the protocol to test three different aspects of frontal brain activation using fNIRS: (1) changes associated with the performance of walking while dual tasking vs. single tasking, (2) changes associated with walking with cognitive vs. motor load, and (3) changes associated with walking with simple vs. complex cognitive load. All of these tasks are associated with activation of the dorso-lateral prefrontal cortex (DLPFC). As such, the fNIRS probes were located on the DLPFC, more specifically on BA 10, a region involved in various executive functions associated with multitasking and planning (Bonelli & Cummings, 2007).

### 5.5.1 Changes in HbO<sub>2</sub> during dual tasking vs. single tasking

Changes in frontal lobe activation during walking while dual tasking have been reported in the literature (Holtzer et al., 2011; Mirelman et al., 2014). Activation of the frontal lobe during walking while talking and walking while serially subtracting 7s was seen in healthy young subjects using fNIRS (Holtzer et al., 2011; Mirelman et al., 2014). In line with these findings, we observed significant increase in frontal activation during

walking while subtracting 3s compared to usual walking in healthy older adults. During the performance of usual walking and standing while subtracting 3s, two tasks that formed the dual task walk, a significant increase in HbO<sub>2</sub> level was seen compared to quiet standing. This increased activation was similar in both single tasks and yet significantly lower than the increased activation observed during the performance of both tasks simultaneously (Table 19). This finding supports the idea that BA 10 plays an important role in the execution of dual task in healthy older adults.

In contrast, persons with PD did not show a significant increase in HbO<sub>2</sub> levels during walking while subtracting 3s, as compared to usual walking (Table 19). Examination of task performance included evaluation of the cognitive task of subtracting 3s, and dual task cost for gait speed and stride length. The results show that their inability to increase frontal lobe activation during walking while subtracting 3s was associated with lower performance of the cognitive task and higher dual task cost for gait speed and stride length, compared to healthy older adults (Table 20).

#### 5.5.1.1 Theoretical explanations

These findings can be explained by the bottleneck theory in which both tasks, walking and subtracting 3s, require the same mechanism at the same time point. Therefore, a bottleneck results, frontal activation cannot be increased, and one or both tasks are impaired. Although the level of HbO<sub>2</sub> did not increase during walking while subtracting S3 in



persons with PD, a significant increase in HbO<sub>2</sub> was observed during usual walking compared to quiet standing. Increased level of HbO<sub>2</sub> during usual walking was also observed in healthy older adults however, comparison between the two groups revealed that persons with PD presented higher frontal activation during usual walking (Table 19).

The increased frontal activation already during usual walk may be explained by the capacity sharing theory. The compensatory mechanisms activated during usual walking are called into play to enhance task performance, but limited capacity diminishes the ability to increase activation while performing additional task. The lower scores of persons with PD in the cognitive tests (Table 5) may reflect the reduced capacity of their neural networks associated with the disease pathology. However, the explanation is likely more complex. Similar to walking while subtracting 3s, HbO<sub>2</sub> levels during standing while subtracting 3s increased compare to quiet standing in healthy older adults but did not change in persons with PD. No significant change in HbO<sub>2</sub> during both tasks that possess higher cognitive load (subtracting 3s) may indicate that persons with PD have also difficulties in recruiting the frontal lobe.

#### 5.5.1.2 HbO<sub>2</sub> level during dual tasking vs single tasking in relation to hypothesis

We hypothesized that level of HbO<sub>2</sub> will be higher during walking while subtracting 3s than usual walking in both groups. The increased frontal activation during walking while subtracting 3s in healthy older adults support this hypothesis. However, the absence of a significant increase in

HbO<sub>2</sub> in persons with PD contradict this hypothesis. Inability to increase frontal activation also during standing while S3 and low performance in the cognitive task suggest that persons with PD have difficulties in recruiting the frontal lobe while performing cognitive task as serially subtracting 3s.

#### 5.5.2 Changes in HbO<sub>2</sub> during walking with motor vs. cognitive load

Walking in real life environments require the ability to manage different types of DT interferences. In the present study, we investigated two types of interference tasks: (1) obstacle negotiation, a motor interference and (2) serially subtracting 3s, a cognitive interference. Comparison between walking while subtracting 3s, a cognitive dual task, and walking while negotiating obstacles, a motor dual task, showed that healthy older adults activated the frontal lobe to a greater extent during the performance of cognitive dual task (Table 19). This finding is in line with the literature in which higher dual task cost was observed during cognitive dual task than during motor dual task (Al-Yahya et al., 2011; Chawla, Walia, Behari, & Noohu, 2014; O'Shea et al., 2002).

In contrast, persons with PD demonstrated significant increased activation during walking while negotiating obstacles, a motor dual task, and not during subtracting 3S, a cognitive dual task (Table 19). These findings contradict Chawla et al. (Chawla et al., 2014) that demonstrated higher dual task cost during cognitive dual task, compared to motor dual task also in persons with PD. These discrepancies may be related to the nature of the motor task being performed. While moving coins from one

pocket to another was the motor task in Chawla et al. study (Chawla et al., 2014) we used negotiating obstacles as the secondary motor task. Obstacle negotiation requires planning and scanning before reaching the obstacles and therefore may involve higher cognitive demands compare to moving coins from one pocket to another. Yet, higher activation of the frontal lobe during obstacle negotiation compare to usual walking and not during subtracting 3s compare to usual walking is surprising.

#### 5.5.2.1 Possible explanations

Possible explanation is that the obstacles acted as an external cue that activate cognitive and attentional networks required to compensate for basal ganglia dysfunction and loss of gait automaticity (Galna et al., 2010). The increased activation in the frontal lobe during walking while negotiating obstacles provide an evident to the alteration in brain activation and facilitation of compensatory mechanism by external cues (Azulay, Mesure, & Blin, 2006; Nieuwboer, 2008). Sensory cues have been shown to improve walking performance and reduce freezing of gait in persons with PD. It is possible that the obstacles presented in the walking path were used as spatial external cues that draw attention to the stepping process. Cueing strategies have shown to improve gait in people with PD and are argued to bypass the defective basal ganglia by using alternative pathways unaffected by PD pathology (Nieuwboer, 2008; Rochester et al., 2005).

These findings are in line with the fMRI results that showed higher activation in frontal regions during imagined walking while negotiating obstacles compare to imagine usual walking in persons with PD (Table 17). However, increased activation in frontal structures during imagined walking while negotiating obstacles was also observed in healthy older adults (Table 16). The fact that motor imagery of gait is primarily a cognitive task that requires increased frontal activation may explain this increased activation also in healthy older adults.

#### 5.5.2.2 HbO<sub>2</sub> level during motor vs cognitive dual tasking in relation to hypothesis

We hypothesized that level of HbO<sub>2</sub> will be higher during walking with cognitive load (subtracting 3s) than walking with motor load (negotiating obstacles) in both groups. Higher frontal activation during walking while subtracting 3s compared to walking while negotiating obstacles in healthy older adults supports this hypothesis. However, increased frontal activation during walking while negotiating obstacles and not during subtracting 3s in persons with PD contradicts this hypothesis. A possible explanation is that in persons with PD the obstacles act as visual cues that facilitates frontal activation.

#### 5.5.3 Changes in HbO<sub>2</sub> during walking with simple vs. complex cognitive load

Comparison between the walking tasks as a function of cognitive load revealed different pattern of activation between the two groups. In the healthy older adults, HbO<sub>2</sub> levels were higher during walking while

counting compare to usual walking, and higher during walking while subtracting 3s compare to usual walking (Table 19). These findings are similar to those shown in healthy young subjects (Mirelman et al., 2014), suggesting that frontal activation during walking while carrying out an additional task reflects task complexity. In contrast, persons with PD presented different pattern of frontal activation. Level of HbO<sub>2</sub> during walking while counting was higher than usual walking, while level of HbO<sub>2</sub> during walking with subtracting 3s was similar to usual walking (Table 19).

#### 5.5.3.1 Possible explanations

These surprising findings may suggest that walking while counting act as an external cue that facilitated frontal activation to improve performance. Dual task cost for stride length and gait speed were suggested to assess performance of walking while dual tasking. Interestingly, we found that walking while counting reduced the dual task cost on stride length. This stands in contrast to the high dual task cost on stride length observed during walking while subtracting 3s (Table 20). As such, it is possible that the counting task act as an auditory external pacer, a cue shown to improve gait and overcome freezing of gait in persons with PD (Nieuwboer, 2008; Rochester et al., 2005).

#### 5.5.3.2 HbO<sub>2</sub> level during complex vs simple cognitive task in relation to hypothesis

We hypothesized that level of HbO<sub>2</sub> will be higher during walking with complex cognitive load (subtracting 3s) than walking with simple cognitive load (counting forward) in both groups. Higher frontal activation

during walking while subtracting 3s compared to walking while counting forward in healthy older adults supports this hypothesis. However, increased frontal activation during walking while counting forward and not during subtracting 3s in persons with PD contradict this hypothesis. Possible explanation is that in persons with PD the counting act as an auditory cue that facilitate frontal activation.

#### 5.5.4 Summary of fNIRS findings

Altogether, our findings indicate that walking in complex situations activate frontal regions in both groups. However, the distribution of frontal activation in the different tasks differs between the groups. Healthy older adults presented graded increase in frontal activation as the cognitive load of the task rise. Standing while subtracting 3s and usual walking showed the lowest level of frontal activation, which increased during walking while counting and walking while negotiating obstacles, and reached to the highest level during walking while subtracting 3s (Figure 23). In contrast, persons with PD presented the lowest level of activation during standing while subtracting 3s, which increased during usual walking and walking while subtracting 3s, and reached to the highest level during walking while counting and walking while negotiating obstacles (Figure 24).

Three possible explanations can be given to the altered pattern of frontal activation observed in persons with PD:

1. **Low efficiency of the neural networks.** High level of frontal activation already during usual walking provides evidence to the

low efficient network of persons with PD that requires the use of cognitive resources to ameliorate the impaired motor function. This low-efficiency network along with reduced cognitive abilities associated with PD pathology limit the neural network capacity. Low capacity may explain the inability to increase frontal activation during walking while dual tasking.

2. **Difficulty in recruiting the frontal lobe.** The increased level of frontal activation during walking while counting and walking while subtracting 3s demonstrate that the level of activation seen during usual walking and subtracting 3s walking is actually not the maximal possible. Inability to increase frontal activation during standing while subtracting 3s and walking while subtracting 3s may explain the low performance in the cognitive task and the high dual task cost for gait speed and stride length in persons with PD compared to healthy control (Table 20).
3. **Sensory cues facilitate frontal lobe activation.** The increased frontal activation during obstacle walking and counting walking show that using appropriate cues may enable higher activation of the frontal lobe. Higher frontal activation was found to be associated with better performance.

The fMRI results support these explanations as the only imagined walking task that healthy older adults showed higher frontal activation than persons with PD was during navigation walk, a task that possess high cognitive load. In addition, the fact that higher frontal activation during

imagined walking tasks was correlated with better performance in motor-cognitive tests in persons with PD (Table 21 and 23) suggests that frontal activation is essential to perform walking while dual tasking.

## 5.6 The fMRI and fNIRS results in the context of cognitive reserve

Persons with PD performed significantly lower than healthy older adults in all cognitive and mobility assessments (Table 5). Lower scores in different cognitive domains and mobility tests along with reduced gait speed and stride length, characterized the group of persons with PD. In addition, disease duration was correlated with disease severity as indicated from the UPDRS ( $r=0.627$ ,  $p=0.009$ ), and with global cognitive score (GCS) ( $r=0.535$ ,  $p=0.033$ ) as obtained from the computerized cognitive tests. These findings provide the behavioral evidences to alterations in brain networks activation, observed in persons with PD.

The differences in brain activation between healthy older adults and persons with PD presented in this study can be explained, perhaps, using the concept of cognitive reserve (Stern, 2012). As such, the results will be discussed according to four ideas: (1) network efficiency, (2) network capacity, (3) neural compensation, and (4) neural reserve.

### 5.6.1 Network efficiency

Network efficiency can be quantified as the differences in activation between subjects that perform similar tasks. Subjects who have adequate performance while utilizing higher levels of activation may have reduced network efficiency. According to this definition, comparisons between



healthy older adults and persons with PD revealed lower network efficiency in persons with PD during both real and imagined usual walking. Performance of imagined usual walking in the MRI scanner showed increased activation in occipital, frontal, parietal, and limbic regions in the persons with PD compared to healthy older adults. This increased activation during the performance of the easiest imagined walking task highlights the low efficiency of the neural network in persons with PD. Similar results were observed in the frontal lobe during real performance of usual walking using the fNIRS system. Comparison between the groups showed increased frontal activation in persons with PD already during real usual walking. In addition, persons with PD showed lower gait speed and reduced stride length compared to healthy older adults. The increased frontal activation during usual walking and the reduced quality of gait in persons with PD emphasizes the low efficiency of their neural network.

#### 5.6.2 Compensatory mechanism

The reduced efficiency of neural networks requires recruitment of compensatory mechanisms. In this study only the fMRI assessments could be used to investigate compensatory mechanisms across all brain regions, as the fNIRS system covers only superficial frontal areas. As shown, both groups activated similar networks during imagined usual walking. However, persons with PD had increased activation in these networks compared to healthy older adults, to be able to perform the tasks. These results show that during imagined usual walking compensatory

mechanisms that include higher activation in common networks are activated in persons with PD.

The fact that we could only measure activation of specific frontal area during real walking limit our ability to draw conclusions regarding activation of compensatory mechanisms during real walking. Further studies that monitor additional brain areas during the performance of dual task walking are needed.

### 5.6.3 Network capacity

The low capacity network of persons with PD is demonstrated in the imagined walking while navigating task. This task possessed the highest cognitive load and in accordance it was the only task in which healthy older adults demonstrated higher activation than persons with PD. As shown in other studies high capacity network will demonstrate that increasing the challenge of the task will result in higher activation in the primary network (Stern, 2012). In line with this assumption, healthy older adults showed increased activation in similar networks during the performance of imagined walking while navigating as during usual walking. However, this was not the case in persons with PD who demonstrated decreased activation in the primary networks. In addition, persons with PD demonstrated poorer performance on the navigation task, only 53% of the responses were correct in persons with PD compare to 90% of correct responses in healthy older adults. The reduced activation of the neural

networks and the poor performance in the navigation task may reflect the low network capacity in persons with PD.

Additional evidence to the low capacity of the system can be drawn from the fNIRS results that show that persons with PD could not increase frontal activation during the performance of walking while subtract 3s, the walking task with the highest cognitive demands.

#### 5.6.4 Neural reserve

PD pathology is associated with massive loss of neurons in the brain. As such, the cognitive reserve of persons with PD is lower than healthy older adults (Hindle, Martyr, & Clare, 2014). According to the cognitive reserve theory, the performance of a task will activate one primary network across different groups of subjects and a secondary compensatory network in patients with reduced cognitive reserve (Hindle et al., 2014; Stern, 2012). Interestingly, higher activation of the secondary network has been associated with lower performance (Steffener, Brickman, Rakitin, Gazes, & Stern, 2009). The reduced cognitive reserve associated with PD and the increased activation in various networks already during a simple task is indicative of the diminished reserve available in these persons with PD. As suggested in the literature, we reasoned that there is a common point in all people where activation reaches a maximum and function cannot be maintained (Stern, 2012). Our fMRI and fNIRS results demonstrate that persons with PD reach this point

sooner limiting their ability to perform more complex tasks needed in everyday life.

All together, the fMRI and fNIRS findings, may indicate that increased brain activation may be a possible strategy to overcome deficits but it may not be sufficient when reaching a certain point of task difficulty in which activation cannot be further increased. The high brain activation observed in persons with PD already during usual walking and the inability to increase activation during highly demanding task as navigation or subtracting 3s reflect a ceiling effect that limit the ability to increase activation during tasks that are more difficult. The breaking point, in which activation cannot longer increase as a function of task difficulty, can be studied using a paradigm that gradually increases task difficulty. For example, gradually increasing the dimensions of the obstacles or the number of intersections that need to be memorized.

Possible way to overcome these problems is to reduce brain activation during simple task as usual walking. Lower activation will increase the brain reserves allocated for more complex tasks as serially subtracting 3s and walking while navigating.

## 5.7 Clinical applications

These results provide some considerations that can be implemented in clinical practice to increase the safety of persons with PD when they ambulate in everyday life environments. These considerations include:

1. Reduce competing stimulus during walking in daily environments. Performing usual walking in persons with PD result in higher activation in frontal, parietal, and occipital regions compare to healthy older adults. The use of more brain resources to perform simple walking may indicate that smaller brain reserves are available for more complex walking tasks as walking while dual tasking. As such we should instruct persons with PD to focus on their walking task without performing additional tasks as talking over the phone or carry things. Our message to them should be to try and minimize the distractions during walking in daily environments.
2. On the other hand unexpected events may occur while walking and therefore we should train our patients to be able to response effectively and reach their target. For that aim training should include walking in complex situations as dual tasking, obstacle negotiation, and navigation while being supervised. In contrast to point 1, this training should be challenging and provocative as the subject's safety is assured by the trainer. Practicing different situations that may occur in daily life may help patients to cope with them in real time. In addition, it is possible that training of complex walking situations increases the efficiency of brain activation resulting in lower activation during usual walking. As shown, better performance was associated with higher activation in persons with PD. Therefore,

lowering brain activation level during usual walking will increase brain reserves that will allow higher activation during complex walking and better performance correspondingly.

3. External cuing, visual cues as obstacles and auditory cues as counting, may facilitate higher frontal activation that is associated with better performance. However, the high brain activation found already during usual walk demonstrate that the use of cues will be most effective if we will find a way to reduce brain activation at baseline (usual walk).
4. Recommend motor-cognitive training on a daily basis to increase cognitive reserve. For example, use different computerized cognitive programs, participate in training groups that include balance, stretching, and strengthening exercises. Although no formal guidelines have been demonstrated in the literature, accumulating evidence show the positive effects of motor-cognitive training on different symptoms associated with aging and PD pathology (de Bruin et al., 2010; Mirelman et al., 2011; Buccello-Stout et al., 2008).

Taken together, we should instruct our patients to discriminate between two situations: daily life and training session. In daily life situations they should focus on the walking task while eliminating possible interferences. In contrast, during training sessions, task complexity should be increased gradually, aiming to reach the breaking point.

## 5.8 Limitations and future directions

Since real walking cannot be performed in the MRI scanner, motor imagery of gait was used. Although this method is commonly used in the literature, it raises several concerns. First, the performance of motor imagery of walking is difficult to validate and measure objectively. Therefore, the actual performance of imagined walking can only be quantified based on subjective report of the subjects. Although similarity between real walking and motor imagery of walking was shown in the literature, it is not clear how well imagined walking represents real walking and how far we can extend the conclusions to real walking.

The velocity of the optic flow used for presenting the virtual environments was set to 1.2 m/sec, the normal walking speed of healthy older adults (Graham, Ostir, Fisher, & Ottenbacher, 2008). However, the mean walking speed of both groups, as observed during the gait assessment was lower. The discrepancies between imagined walking speed and velocity of virtual environment may change the ability to perform motor imagery. Future studies should adjust the velocity of the virtual environment to the real walking speed of the participants.

Although both groups had adequate motor imagery ability, as measured with the KVIQ and chronometric tests, the persons with PD reported greater difficulty imagining themselves walking and lower level of engagement during the imagined tasks, compared to the healthy older adults. These difficulties to perform imagined walking may be the reason for the higher brain activation in persons with PD, compared to healthy

older adults. However, one can also argue that if they did poorly on motor imagery, they would activate less. In order to address these limitations, we used fNIRS system that can measure frontal activation in real performance of walking. However, the fNIRS system that was used in this study included only two probes that were located specifically on BA 10 which is considered part of the DLPFC. Having two probes placed only on the forehead limits our ability to show that the observed pattern of activation is specific to BA 10. Future studies should include an fNIRS system with more probes that will be located on different brain areas.

The inclusion criteria for persons with PD were Hoehn and Yahr stages II-III (Hoehn & Yahr, 1967). Persons with PD in this range of H&Y can present different levels of cognitive and motor impairments that can be associated with different patterns of brain activation. Future studies should evaluate the differences in brain activation during imagined walking between subgroups of persons with PD that present different motor-cognitive deficits. Differences in brain activation between these two subgroups may provide insight into specific interventions that best address the impairments of each group.

The performance of obstacle crossing was measured using the distance of toe from obstacle and obstacle from heel. We encountered difficulties in attaining accurate measurements that reflect performance. For example, inability to measure the distance when subject hit the obstacle, and small variances in placing the obstacles. Future studies



should consider different methods to evaluate the performance of stepping over obstacles.

No changes in activation during imagined walking were observed in subcortical regions within and between groups. Since one of the main hallmarks of Parkinson's disease is a major loss of dopaminergic cells in substantia nigra, we hypothesized to find different activation in basal ganglia between the groups. Future studies should include ROI analysis of the basal ganglia to better understand the role of these region in walking in complex situations and better defined changes in these region between groups.

The correlations between brain activation and motor-cognitive performance differ between the tasks. We speculate that task difficulty has a direct impact on these changes in correlations. Future studies should involve tasks in which difficulty can be gradually increased. That will help us to define the breaking point in which patterns of activation are altered.

## 5.9 Summary

The results of this study provide new understandings of the underlying mechanisms of gait in healthy older adults and persons with PD. Although, similar networks were activated in both groups the pattern of activation and the correlation with motor-cognitive performance were different. These findings can explain the difficulties that persons with PD encounter in every-day life and provide evidence to the high fall risk of persons with PD.

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